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Protocol-specific Sponsor Contact information can be found in the Investigator Trial File Binder (or equivalent).

TITLE:

A Phase Ib Study of Pembrolizumab (MK-3475) in Chinese Subjects with Locally Advanced or Metastatic Melanoma (Keynote-151)

EudraCT NUMBER: Not Applicable

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SUMMARY OF CHANGES

PRIMARY REASON(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
2.1	Trial Design	To quantify time duration to number of cycles: 24 weeks to 8 cycles; 12 months/1 year to 17cycles; 24 months/2 years to 35 cycles	To accurately describe the treatment in terms of cycles instead of duration.
2.2	Trial Diagram	To quantify time duration to number of cycles: 24 weeks to 8 cycles; 12 months/1 year to 17cycles; 24 months/2 years to 35 cycles	To accurately describe the treatment in terms of cycles instead of duration.
5.1.2	Subject Inclusion Criteria(12.13.14)	Update language for contraception	Make the criteria more concise and follow Merck's standard language in pembrolizumab studies.
5.1.3	Subject Exclusion Criteria	Change exclusion criteria from "Has history or evidence of active pneumonitis" to "Has a history of (non-infectious) pneumonitis that required steroids or current pneumonitis"	Make the language more precise regarding pneumonitis and consistent with the standard required text in Merck's pembrolizumab studies.

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
5.2.1.2	Dose Modification(Escalation/Titration/Other)	Added that treatment should be permanently discontinued for recurrent Grade 2 pneumonitis. Added dose medication guidance and foot note for Grade 2 infusion reaction.	The current language for permanently discontinuation due to recurrent Grade 2 pneumonitis and grade 2 infusion reaction are not present in old Table 3. This revision is to emphasize permanently discontinuation for recurrent Grade 2 pneumonitis and dose modification for infusion reaction to align with Merck's standard required language for pembrolizumab studies.
5.8	Subject Withdrawal/Discontinuation Criteria	Update language for discontinuation from treatment to align with current protocol template languages	For patient's safety sake, we updated discontinuation criteria based on latest safety information of Pembrolizumab and accurately describe the treatment in terms of cycles instead of duration.
5.8.1	Temporary Discontinuation of Study Therapy after CR	To quantify time duration to number of cycles: 24 weeks to 8 cycles; 12 months/1 year to 17 cycles	To accurately describe the treatment in terms of cycles instead of duration.
6.0	TRIAL FLOW CHART	To clearly state in trial flow chart that the second course phase is maximum up to 17 cycles	Updated the flowchart to make the protocol more clear and feasible.

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
6.0	TRIAL FLOW CHART	Update footnote 3 for survival follow-up	Updated the footnote for survival follow-up to make it more clear and feasible.
7.1.5.2.1	Second Course Phase (Retreatment Period)	To quantify time duration to number of cycles: 24 weeks to 8 cycles; 12 months/1 year to 17 cycles; 24 months/2 years to 35 cycles	To accurately describe the treatment in terms of cycles instead of duration.
7.1.5.2.1	Second Course Phase (Retreatment Period)	Subject enters second course phase treatment need to have SPONSOR approval.	To ensure the subject eligibility and for subject's safe. This is also aligned with Merck other melanoma studies (KEYNOTE002,006)
7.1.5.2.1	Second Course Phase (Retreatment Period)	Adding the sentence "A scan documenting PD should be performed within 4 weeks prior to starting Second Course treatment." following the sentence "Experienced an investigator-determined confirmed radiographic disease progression after stopping their initial treatment with MK-3475."	To add the time window for imaging scan prior to starting Second Course treatment which is consistent with the Trial Flow Chart.

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
7.1.2.6.2	Tumor Imaging During Trial	Adding the sentence "Subjects will then return to regular scheduled imaging, starting with the next scheduled imaging time point. Subjects who obtain a confirmation scan do not need to undergo the next scheduled tumor imaging if it is < 4 weeks later; tumor imaging may resume at the subsequent scheduled imaging time point"	Subjects who obtain a confirmation scan do not need to undergo the next scheduled tumor imaging if it is < 4 weeks later. This is for subject's sake, and this is to align with current Merck standard protocol template language for imaging
8.6.2	Statistical Methods for Safety Analyses	Delete analysis of 95% confidence interval for AE incidence rate.	For single arm study, 95% confidence interval will not be provided for AE incidence rate.
12.2	ECOG Performance Status	Update the ECOG table with the correct version	Correct the ECOG table with the right version

ADDITIONAL CHANGE(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
5.11	Clinical Criteria for Early Trial Termination	Update languages to be aligned with current protocol template languages	Text updated to align with current Merck standard protocol template language. This is to give clear guidance for the early trial termination.
6.0	TRIAL FLOW CHART	Update Report all ECIs occurring up from "until 90 days" to "until 30 days" in footnote 6 in section 6.1 and footnote 5 in section 6.2	It should be 30 days. This is an inconsistence error.
7.2.3.1	Serious Adverse Events	Update "Table 7" to "Table 6"	Correct error
7.2.3.3	Protocol-Specific Exceptions to Serious Adverse Event Reporting	Delete the sentence" Immediate Reporting of Adverse Events to the Sponsor, unless there is evidence suggesting a causal relationship between the drug and the event. Any such event will be submitted to the Sponsor within 24 hours either by electronic or paper media." Which should be removed based on standard protocol template languages	It should be deleted. This is an error.

No additional changes.

1.0 TRIAL SUMMARY

Abbreviated Title	Phase Ib Study of MK-3475 in Chinese Subjects with Advanced Melanoma
Trial Phase	Ib
Clinical Indication	The treatment of subjects with locally advanced or metastatic melanoma with disease progression following previous first line chemotherapy therapy
Trial Type	Interventional
Type of control	No treatment control
Route of administration	Intravenous
Trial Blinding	Unblinded Open-label
Treatment Groups	MK-3475 2 mg/kg every 3 weeks (Q3W)
Number of trial subjects	Approximately 80 subjects will be enrolled.
Estimated duration of trial	The Sponsor estimates that the trial will require approximately 12-24months from the time the first subject signs the informed consent until the last subject's last study-related phone call or visit.
Duration of Participation	Each subject will participate in the trial from the time the subject signs the informed consent form (ICF) through the final protocol-specified contact. After a screening phase of 28 days, each subject will be assigned to receive trial treatment until disease progression is confirmed by the site per immune related Response Evaluation Criteria in Solid Tumors (irRECIST), unacceptable adverse event(s), intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw the subject, noncompliance with trial treatment or procedures requirements or administrative reasons requiring cessation of treatment, or until the subject has received 35 administrations of pembrolizumab (approximately 2 years). Subjects who stop trial treatment after receiving 35 administrations of pembrolizumab for reasons other than disease progression or intolerability, or subjects who attain a complete response and have been treated for at least 24 weeks, and stop trial treatment may be eligible for up to 17 additional administrations of pembrolizumab (approximately one year) upon experiencing disease progression. After the end of treatment, each subject will be followed for the occurrence of adverse events as described under section 7.1.5.4.1 of the protocol. Subjects who discontinue for reasons other than disease progression will have post-treatment follow-up for disease status until disease progression is confirmed by the site per irRECIST, initiating a non-study cancer treatment, withdrawing consent, or becoming lost to follow-up. All subjects will be followed every 12 weeks by telephone for overall survival until death, withdrawal of consent, or the end of the study. .

A list of abbreviations used in this document can be found in Section 12.8.

2.0 TRIAL DESIGN

2.1 Trial Design

This is an open-label, non-randomized, multi-center, Phase Ib study of MK-3475 in Chinese subjects with advanced melanoma to be conducted in conformance with Good Clinical Practices. Approximately 80 subjects will be enrolled in this trial to examine the safety and efficacy of the 2 mg/kg dose of MK-3475 administered every 3 weeks. The primary objectives of the trial are to determine the safety, tolerability, and overall response rate (ORR) per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) in Chinese subjects with advanced melanoma. Pharmacokinetics will also be characterized in this study by having additional blood collected from 30 subjects. Subjects will be evaluated every 6 weeks starting at 12 weeks through 48 weeks, and after 48 weeks, every 12 weeks with radiographic imaging to assess response to treatment. Tumor response will be assessed using RECIST 1.1 by the central independent radiology review. RECIST 1.1 as assessed by the central imaging vendor will be used to determine eligibility and immune-related RECIST (irRECIST) will be used to make treatment decisions (refer to Section 4.2.3.2). Adverse events will be monitored throughout the trial and graded in severity according to the guidelines outlined in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

Treatment with MK-3475 will continue unless the subject meets the discontinuation criteria such as disease progression (evaluated by irRECIST), unacceptable toxicity, or completion of 35 cycles (approximately 24 months) of treatment with MK-3475 (refer to Section 5.8 for further details). Subjects who attain an investigator-determined confirmed CR may consider stopping trial treatment after receiving at least 8 cycles (approximately 24 weeks) of treatment (Treatment Phase). Subjects who discontinue after attaining a CR or who complete 35 cycles (approximately 24 months) study treatment may be eligible for up to 17 cycles additional (approximately 1 year) of retreatment (Second Course Phase) after they have experienced radiographic disease progression. The decision to retreat will be at the discretion of the investigator only if no cancer treatment was administered since the last dose of MK-3475, the subject still meets the safety parameters listed in the Inclusion/Exclusion criteria and the trial remains open (refer to Section 7.1.5.2.1 for further details). After the end of treatment in Treatment Phase and Second Course phase, each subject will be followed for 30 days for adverse event monitoring (serious adverse events and events of clinical interest will be collected for 90 days after the end of treatment). Subjects who discontinue treatment for reasons other than disease progression will have post-treatment follow-up for disease status until initiating a non-study cancer treatment, disease progression, withdrawing consent, death, or the end of the study, whichever occurs first. Response and progression in the Second Course Phase will not count towards the ORR and Progression Free Survival (PFS) of the efficacy endpoint in this trial. All subjects will be followed by telephone contact for overall survival until death, withdrawal of consent or the end of the study, whichever comes first.

Participation in this trial will require submitting an archival tissue sample or newly obtained biopsy of a tumor lesion not previously irradiated for PD-L1 expression evaluation. This specimen will be evaluated at a central laboratory for expression status of PD-L1 by

immunohistochemistry (IHC). Both PD-L1 positive and negative subjects will be enrolled in this trial, and the clinical activity in both subsets will be evaluated as a pre-defined subgroup analysis.

Specific procedures to be performed during the trial, as well as their prescribed times and associated visit windows, are outlined in the Trial Flow Chart - Section 6.0. Details of each procedure are provided in Section 7.0 – Trial Procedures.

2.2 Trial Diagram

The trial design is depicted in Figure 1 below.

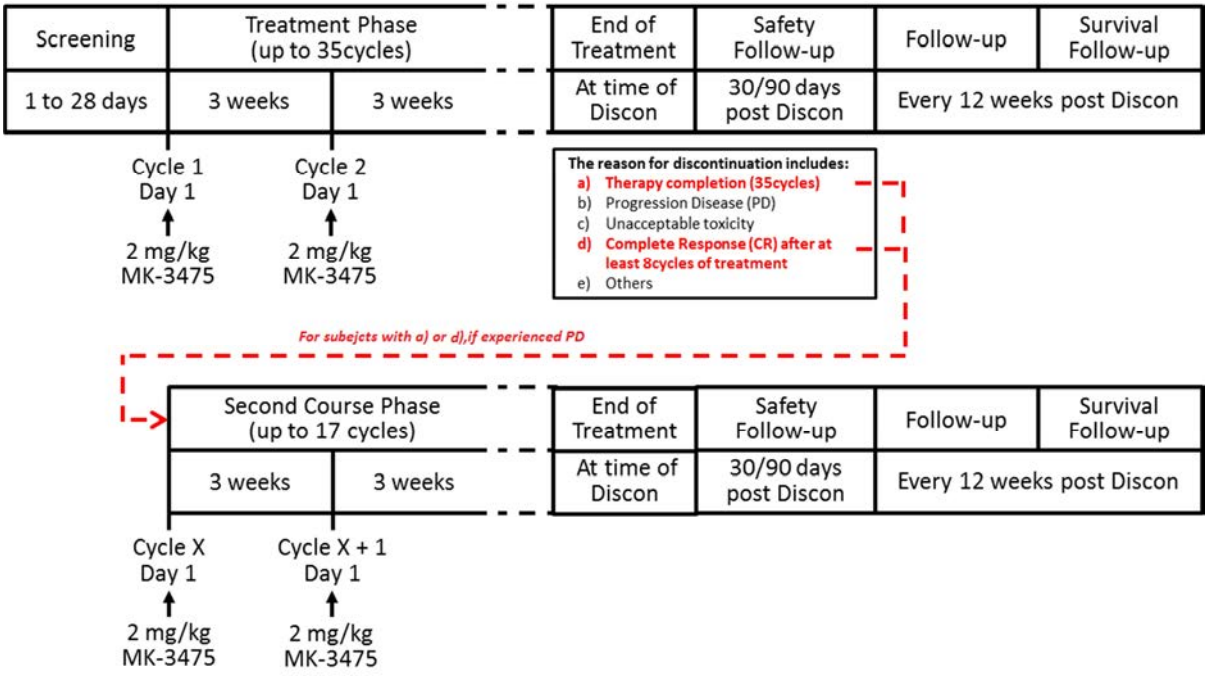

Figure 1 Trial Design Diagram

3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

3.1 Primary Objective(s) & Hypothesis(es)

At a 2 mg/kg Q3W dose of MK-3475 in Chinese subjects with advanced melanoma:

1) **Objective:** To determine the safety and tolerability.
2) **Objective:** To evaluate the ORR based on RECIST 1.1 assessed by the central independent radiology review.

   Hypotheses: The ORR per RECIST 1.1 by the central independent radiology review is greater than ORR from historical control (10%).

3.2 Secondary Objective(s) & Hypothesis(es)

At a 2 mg/kg Q3W dose of MK-3475 in Chinese subjects with advanced melanoma:

1) **Objective:** To evaluate the duration of response (DOR) and PFS per RECIST 1.1 and irRECIST by central independent radiology review, ORR per irRECIST by central independent radiology review and OS.
2) **Objective**: To evaluate the pharmacokinetic (PK) profile.

4.0 BACKGROUND & RATIONALE

4.1 Background

Refer to the Investigator's Brochure (IB) for detailed background information on MK-3475.

4.1.1 Pharmaceutical and Therapeutic Background

MK-3475 is a potent and highly selective humanized monoclonal antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between PD-1 (programmed cell death-1) and its ligands PD-L1 and PD-L2. This blockade enhances functional activity of the target lymphocytes to facilitate tumor regression and ultimately immune rejection. Targeting PD-1 has been emerged as one of the most advances for treatment of melanoma evidenced by break-through approval by US FDA for pembrolizumab (MK-3475) in September 2014 and similar mAb against PD-1, Nivolumab, has also been approved in Japan in 2014.

The PD-1 pathway represents a major immune control switch which may be engaged by tumor cells to overcome active T-cell immune surveillance. The normal function of PD-1, expressed on the cell surface of activated T-cell under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 is an Ig superfamily member which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) [1, 2]. Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. High expression of PD-L1 on tumor cells (and to a lesser extent of PD-L2) has been found to correlate with poor prognosis and survival in various cancer types including renal cell carcinoma (RCC), pancreatic carcinoma, hepatocellular carcinoma, ovarian carcinoma and non-small-cell lung cancer (NSCLC) [3-6]. Furthermore, PD-1 has been suggested to regulate tumor-specific T-cell expansion in subjects with melanoma [7]. This suggests that the PD-1/PD-L1 pathway plays a critical role in tumor evasion and is thus an attractive target for therapeutic intervention.

Melanoma is a malignant tumor of melanocytes, which are the cells that create the pigment melanin and are derived from the neural crest. Although melanoma accounts for less than 5% of skin cancer cases; it is the most lethal form and accounts for over 75% of skin cancer deaths [8]. Internationally, approximately 160,000 new cases of melanoma are diagnosed per year, with over 70% of these diagnosed in Australia, Europe, or North America [9-10]. In China, approximately 9418 new cases of skin melanoma were diagnosed and approximately 6154 people died of melanoma in 2012 [Globocan 2012, IARC]. The incidence of melanoma is increasing worldwide, with a growing fraction of subjects with advanced disease for which

prognosis remains poor. The median survival for subjects with locally advanced and metastatic melanoma has been under 1 year. The 5-year survival rate of patients with visceral involvement is under 10% and the goal of treatment for this incurable condition is palliative with marginal survival benefit [11].

Comparing to Western countries, there is a relatively high number of more mucosal (22.6%) and acral melanoma (50.8%) reported in China [12]. Mucosa melanoma tends to have poor prognosis. The treatment option for advanced melanoma in China is very limited and the standard first therapy in China is limited to dacarbazine. More effective treatment options such as ipilimumab (IPI) are not available in China. The overall prognosis of melanoma in China is worse than that of western countries, so there is an urgent need for new treatment options in China.

Recent data with anti-PD-1 antibodies, including nivolumab (BMS-936558, ONO-4538) and MK-3475, have validated PD-1 as an attractive target for clinical intervention and have provided proof of concept for anti-PD-1 mAbs in melanoma [13-15]. Nivolumab has an observed objective response rate of 28% in melanoma subjects who had not previously received IPI [14]; MK-3475 has shown a promising response rate of 41% in melanoma subjects. Specifically, a response rate of more than 40% was observed with MK-3475 in melanoma subjects who have not received prior IPI treatment [16]. This response rate is much higher than the 11-15% response rate observed in IPI registration trials. Importantly, responses have been of long duration, and both MK-3475 and nivolumab are generally well tolerated. Median overall survival of nivolumab was 16.8 months, and 1- and 2-year survival rates were 62% and 43%, respectively [16-17]. The median overall survival rate in melanoma of MK-3475 KEYNOTE-001 was not reached for the entire study population or for any of the individual dose schedules at the time of the analysis. For all subjects and dose schedules the fraction of subjects alive at one year was more than approximately 80% [see Investigators Brochure (IB)]. Drug related adverse events (AEs) were reported for 340 of 411 (83%) in KEYNOTE-001 (all melanoma subjects: Parts B1+B2+D). The most common drug-related AEs in melanoma subjects, reported in at least 10% of subjects, were: fatigue (36.0%), pruritus (23.8%), rash (19.7%), nausea (12.2%), diarrhea (16.3%), arthralgia (15.6%), and vitiligo (10.7%) (unpublished internal data: as of 18-Oct-2013). Safety data from KEYNOTE-001 indicate that most AEs were typically grade 1-2 in severity and reversible, and that MK-3475 has an acceptable safety profile for the treatment of advanced melanoma subjects.

The US FDA approval for pembrolizumab, STN BL 125514, relies on the results of a single, randomized (1:1), open-label, dose-ranging, multicenter cohort (Cohort B2) within a large, multi-stage, multiple cohort dose-finding, activity-estimating, safety and tolerability trial, Study KEYNOTE-001. This sub-study is comprised of 173 subjects with advanced or unresectable melanoma, who had progressed on or within 24 weeks of receiving ipilimumab and, if their melanoma tumor was BRAF V600 mutation-positive, had also received a prior BRAF inhibitor, and were randomized and received at least one dose of study treatment. All subjects were required to have evidence of active disease progression at the time of enrollment. Key exclusion criteria included the presence of autoimmune disease, requiring for therapeutic corticosteroids (> 10 mg prednisone/day), and severe autoimmune adverse drug reactions with prior ipilimumab therapy.

The trial met its primary endpoint of demonstrating an objective response rate of >10% based on the lower 95% confidence interval around the observed response rate of 24% (95% CI:15,34) according to Response Evaluation Criteria in Solid Tumors (RECIST 1.1) as assessed by blinded independent central review (IRC) which included both radiologists and oncologists.

Durable objective tumor responses were observed at a similar rate with both treatment regimens. Merck requested approval only for the lower dose administered in Cohort B2. The selection of this regimen as the recommended dose is appropriate since the anti-tumor activity was similar between the two arms in Cohort B with respect to both overall response rate and duration of response.

The safety database contained all adverse event information reported in 411 subjects with unresectable or metastatic melanoma who received pembrolizumab administered as an intravenous infusion at doses of 2 mg/kg every 3 weeks or 10 mg/kg every 2 weeks or 10 mg/kg every 3 weeks. This safety information was supplemented by complete safety information from sequential dose- escalation cohorts from Study KEYNOTE-001 and by the serious and unexpected adverse drug reactions reported in approximately 2000 subjects enrolled in completed or ongoing clinical trials of pembrolizumab.

Therefore, clinical development of MK-3475 would have a great significance in patients with advanced melanoma including the IPI-naïve population in China.

4.1.2 Ongoing Clinical Trials

MK-3475 is being studied for various oncology indications including melanoma, non-small cell lung cancer, head and neck cancer, triple negative breast cancer, gastric cancer, bladder cancer, hematologic malignancies and other solid tumors. Two ongoing, randomized studies with active comparators (KEYNOTE-002/ KEYNOTE-006) for melanoma are ongoing. For trial details please refer to the IB.

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

As described in 4.1.1 Pharmaceutical and Therapeutic Background, MK-3475 has shown to be very well-tolerated and efficacious measured by 24% objective response rates in melanoma subjects at clinically approved dose [16]. Also, non-clinical and clinical data obtained so far supports clinical development of MK-3475 in China.

In China, treatment options for locally advanced and metastatic melanoma have been limited to chemotherapeutic agents such as dacarbazine. Outside China, there has been steady progress in the development of targeted therapy and immunotherapy for locally advanced and metastatic melanoma. BRAF inhibitors (vemurafenib and dabrafenib), anti-Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) mAb (IPI), and MEK inhibitor (trametinib) were approved for treatment of locally advanced and metastatic melanoma in the past few years; however these newly therapies have not been approved yet in China. Available treatment options for Chinese patients such as cytotoxic chemotherapies have very limited activity even in the first-line setting. The efficacy rate for darcabazine based regimen is marginal with ORR 7%, PFS 1.6 months and OS (0-6 months). There is no standard regimen for 2nd line

therapy. Thus, the outcome of patients with locally advanced and metastatic melanoma still remains dismal and the development of new effective therapy represent an urgent need.

This is an open-label, non-randomized, multi-center, Phase Ib trial of MK-3475 in Chinese subjects with advanced melanoma. Subjects with prior history chemo-therapy will be enrolled in this trial. All subjects will be required to submit a tumor tissue sample for PD-L1 expression evaluation as a pre-defined subgroup analysis.

Details regarding specific benefits and risks for subjects participating in this clinical trial may be found in the accompanying IB and Informed Consent documents.

4.2.2 Rationale for Dose Selection/Regimen

The dosing regimen of MK-3475 in this study was based on US approved treatment regimen and lack of ethnic difference in regard to the exposure and safety. This dose regimen was supported by the results from the overseas phase I study (KEYNOTE-001, refer to IB), PK of MK-3475 showed slow systemic clearance, limited volume of distribution, and a long half-life (13-21 days). Pharmacodynamic data (IL-2 release assay) suggested durable peripheral target engagement (>21 days). These early PK and pharmacodynamic data provide scientific rationale for testing Q3W dosing schedule. Also, preliminary preclinical data in syngeneic mouse tumor models suggests that sustained inhibition of PD-1 is important for maintaining anti-tumor activity (unpublished internal data). Thus, MK-3475 will be given until disease progression, unacceptable toxicity, or completion of 35 cycles (approximately 24 months) of treatment with MK-3475 in the trial. The only exception is those subjects who experience a confirmed CR; these subjects may discontinue treatment with MK 3475 at the discretion of the investigator (see Section 5.8.1 for details).

KEYNOTE-001 study showed that, when evaluated in a randomized setting (in Cohorts B2 and D), the efficacy of MK-3475 given Q3W is comparable between 2 mg/kg and 10 mg/kg doses, indicating no improvement in efficacy with a 5-fold higher dose of MK 3475 beyond the 2 mg/kg dose (as determined by ORR, PFS, and OS endpoints). Similarly, the safety and AE profile of MK-3475 also appear similar between the 2 mg/kg Q3W and 10 mg/kg Q3W doses. Finally, PK/PD analysis indicates a flat exposure-efficacy relationship beyond the 2 mg/kg dose. Taken together, these analyses indicate that the 2 mg/kg dose is associated with optimal efficacy and safety when MK-3475 is administered on a Q3W schedule for the subjects with advanced melanoma (unpublished internal data).

Preliminary data also revealed lack of ethnic factor on the PK of MK-3475.

4.2.3 Rationale for Endpoints

4.2.3.1 Safety Endpoints

The primary safety objective of this study is to characterize the safety and tolerability of MK-3475 in subjects with advanced melanoma. In addition to general laboratory tests, immune laboratory testing will be evaluated considering the mode of action of MK-3475. The primary safety analysis will be based on subjects who experienced toxicities as defined by

CTCAE criteria. Safety will be assessed by quantifying the toxicities and grades experienced by subjects who have received MK-3475, including serious adverse events (SAEs) and events of clinical interest (ECIs).

Safety will be assessed by reported adverse experiences using CTCAE, Version 4.0. The attribution to drug, time-of-onset, duration of the event, its resolution, and any concomitant medications administered will be recorded. AEs will be analyzed including but not limited to all AEs, SAEs, fatal AEs, and laboratory changes. Furthermore, specific immune-related adverse events (irAEs) will be collected.

4.2.3.2 Efficacy Endpoints

The primary efficacy objective of this study is to evaluate ORR per RECIST 1.1 in subjects with advanced melanoma. The secondary objectives are to evaluate DOR and PFS per RECIST 1.1, ORR, DOR, and PFS per irRECIST, and OS in subjects with advanced melanoma. Response rates per RECIST 1.1 [18] and irRECIST [19] will be evaluated by central independent radiology review. RECIST 1.1 as assessed by the central imaging vendor will be used to determine eligibility and irRECIST will be used to make treatment decisions.

RECIST 1.1 will be adapted to account for the unique tumor response characteristics seen with treatment of MK-3475. Immunotherapeutic agents such as MK-3475 may produce antitumor effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents, and can manifest a clinical response after an initial increase in tumor burden or even the appearance of new lesions. Standard RECIST may not provide an accurate response assessment of immunotherapeutic agents such as MK-3475. Therefore, irRECIST will be used with the adaptations (refer to Section 7.1.2.6.4), in which a confirmation assessment of disease progression must be obtained at least 4 weeks after the initial disease assessment indicating progressive disease.

The irRECIST are a published set of guidelines proposed for immunotherapies in solid tumors. Inclusion of this method is based on the observation that some patients with melanoma may have a transient increase in measured tumor size or small new lesions on Computed Tomography (CT) scans (due to infiltration of inflammatory cells) in the first few months after start of immunotherapy, with subsequent reduction in tumor size (due to immune-mediated tumor cell kill).(refer to Section 7.1.2.6.4)

Rationale for single arm design:

The key objectives for this study are to assess the safety, efficacy in patients with advanced melanoma. The nature of disease is progressive, and with very limited treatment option. Overall response has been commonly used to assess the efficacy of anti-tumor drug in single arm design setting. The study population for this study is patients who failed initial chemotherapy. In China, there is no standard 2nd line treatment for such patient populations. Therefore, no comparator could be used to support a randomized trial. In addition, robust efficacy has been demonstrated in clinical trials leading to US approval, and similar efficacy is anticipated in Chinese and can be reasonably assessed using single arm design initially used in supporting the first approval in US.

Concerning the aggressive nature of disease per se and MK-3475 has been approved oversea based on the robust efficacy demonstrated in previous trials, the subjects may benefit from this trial. Therefore, placebo controlled study has not been considered for this study. Similar approach has been used to support the approval of MK-3475 in US.

In balance of science and ethical consideration, single arm design appears appropriate to meet the objectives of this study.

4.2.3.3 Pharmacokinetic/Immunogenicity Endpoints

Serum samples from 30 patients will be obtained to measure pharmacokinetics of MK-3475. In addition, potential of the formation of anti-MK-3475 antibody will also be evaluated for interpretation of immunogenicity results. The PK endpoints and time points for PK blood sampling are consistent with our previous studies to allow adequate description of PK in this patient population.

4.3 Benefit/Risk

Subjects in clinical trials generally cannot expect to receive direct benefit from treatment during participation, as clinical trials are designed to provide information about the safety and effectiveness of an investigational medicine.

Additional details regarding specific benefits and risks for subjects participating in this clinical trial may be found in the accompanying IB and Informed Consent documents.

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

Male/Female subjects with locally advanced or metastatic melanoma will be enrolled in this trial.

5.1.2 Subject Inclusion Criteria

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

1. Be of the Chinese descent born in China, and have a Chinese home address.
2. Be willing and able to provide written informed consent for the trial.
3. Be ≥ 18 years of age on day of signing informed consent.
4. Have histologically confirmed diagnosis of locally advanced (unresectable Stage III) or metastatic (Stage IV) melanoma not amenable to local therapy.
    - Subject may not have a diagnosis of uveal or ocular melanoma.
    - Overall proportion of subjects with mucosa melanoma will be no more than 22%.
5. Have failed the first line chemotherapy (excluding adjuvant or neoadjuvant therapy) or targeted therapy for melanoma.

6. Have at least one measurable lesion as defined by RECIST 1.1 on imaging studies (CT or MRI).

   Note: Tumor lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions.

   Note: Cutaneous lesions and other superficial lesions are not considered measurable lesions for the purposes of this protocol, but may be considered as non-target lesions.

7. Have a performance status of 0 or 1 on the Eastern Cooperative Oncology Group (ECOG) Performance Scale.

8. Have an anticipated life expectancy of at least 3 months.

9. 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 (without supportive care)
Platelets	≥ 100,000 / mcL
Hemoglobin	≥9 g/dL or ≥5.6 mmol/L (without transfusion or EPO dependent within 7 days)
Renal	
Serum creatinine OR Measured or calculated creatinine clearance (CrCl) a (GFR can also be used in place of creatinine or CrCl)	≤ 1.5 X upper limit of normal (ULN) OR ≥50 mL/min for subjects with creatinine levels > 1.5 X institutional ULN
Hepatic	
Serum total bilirubin	≤ 1.5 X ULN (or < 3x ULN in subjects with Gilbert's syndrome) OR direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 X ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 X ULN OR ≤ 5 X ULN for subjects with liver metastases
Coagulation	
Prothrombin Time (PT) / International Normalized Ratio (INR), activated Partial Thromboplastin Time (aPTT)	≤1.5 X ULN unless the subject is receiving anticoagulant therapy as long as PT or aPTT is within therapeutic range of intended use of anticoagulants
[a] Creatinine clearance should be calculated per institutional standard. If no local guideline is available, Creatinine Clearance should be calculated using the Cockcroft-Gault Method: CrCl = [(140-age) * weight (kg) * (0.85 for females only)] / (72 * serum creatinine)	

10. Have provided tissue for PD-L1 expression evaluation from an archival tissue sample or newly obtained core or excisional biopsy of a tumor lesion not previously irradiated.

    Note: Subjects will be eligible to participate regardless of the level of PD-L1 expression.

11. Have documented BRAF mutation status or be willing to provide a tumor tissue for BRAF genotyping.

    Note: BRAF V600 mutation analysis should be performed at screening in subjects without documented BRAF status.

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

13. Female subjects of childbearing potential must be willing to use an adequate method of contraception as outlined in Section 5.7.2 - Contraception, for the course of the trial through 120 days after the last dose of trial drug.

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

14. Male subjects of childbearing potential must agree to use an adequate method of contraception as outlined in Section 5.7.2 - Contraception, starting with the first dose of trial therapy through 120 days after the last dose of trial therapy.

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

5.1.3 Subject Exclusion Criteria

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

1. Has received prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2 agents.
2. Is currently participating and receiving study therapy or has participated in a study of an investigational agent and received study therapy or used an investigation device within 4 weeks of the first dose of treatment.
3. Has had a prior anti-cancer monoclonal antibody (mAb) within 4 weeks prior to the first dose of trial treatment or who has not recovered (ie., $\leqslant$ Grade 1 or at baseline) from adverse events due to agents administered more than 4 weeks earlier.
4. Has had chemotherapy, targeted small molecule therapy, radiotherapy within 2 weeks prior to the first dose of trial treatment, or who has not recovered ($\leq$ Grade 1 or baseline) from adverse events due to a previously administered agent.

   Note: Subjects with $\leq$ Grade 2 neuropathy or alopecia are an exception to this criterion and may qualify for the study.

   Note: If subject received major surgery or radiation therapy of > 30 Gy, they must have recovered from the toxicity and/or complications from the intervention prior to starting therapy.

5. Has a known history of another (including unknown primary) malignancy within 5 years prior to first study drug administration.

   Note: Exceptions include adequately treated Stage 1 or Stage 2 basal/squamous cell carcinoma of the skin, superficial bladder cancer, or cancer in situ which has undergone potentially curative therapy.

6. Is expected to require any other form of systemic or localized antineoplastic therapy while in study.

7. Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis.

   Note: Subjects with previously treated brain metastases and clinically stable CNS metastases are allowed to participate (clinically stable is defined as a period (at least 4 weeks prior to the first dose of trial treatment) in which (1) there is no evidence of new or enlarging CNS metastases by MRI, (2) the subject is off steroids for at least two weeks, and (3) any neurologic symptoms have returned to baseline).

8. Has active autoimmune disease that has required systemic treatment in past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.

9. Is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 1 week prior to the first dose of trial treatment.

10. Has an active infection requiring intravenous systemic therapy.

11. Has received a live vaccine within 4 weeks prior to the first dose of trial treatment (refer to Section 5.5.2 for further details).

12. Has a known hypersensitivity to the components of the study drug or another monoclonal antibody.

13. Has a history of (non-infectious) pneumonitis that required steroids or current pneumonitis.

14. Is known to be Human Immunodeficiency Virus (HIV)-positive (HIV 1/2 antibodies).

15. Has known active Hepatitis B or C. Active Hepatitis B is defined as a known positive HBsAg result. Active Hepatitis C is defined by a known positive Hep C Ab result and known quantitative HCV RNA results greater than the lower limits of detection of the assay.

16. Has a history or current evidence of any condition, therapy, or lab abnormality that might confound the results of the study, interfere with the subject's participation for the full duration of the study, or is not in the best interest of the subject to participate.

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

18. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the screening visit (Visit 1) through 120 days after the last dose of trial treatment.

5.2 Trial Treatment(s)

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

Table 2 Trial Treatment/Vaccination

Drug	Dose/ Potency	Dose Frequency	Route of Administration	Regimen/ Treatment Period	Use
MK-3475	2 mg/kg	Q3W	IV infusion	Day 1 of each cycle	Experimental

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

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 trial treatments in accordance with the protocol and any applicable laws and regulations.

5.2.1 Dose Selection/Modification

5.2.1.1 Dose Selection (Preparation)

The rationale for selection of doses to be used in this trial is provided in Section 4.0 – Background and Rationale. The dose amount required to prepare the MK-3475 infusion solution will be based on the subject's weight in kilograms (kg). Details on the dose calculation, preparation and administration are provided in the Procedures Manual.

5.2.1.2 Dose Modification (Escalation/Titration/Other)

Adverse events (both non-serious and serious) associated with MK-3475 exposure may represent an immunologic etiology. These adverse events may occur shortly after the first dose or several months after the last dose of treatment. MK-3475 must be withheld for drug-related toxicities and severe or life-threatening AEs as per Table 3 below. See Section 5.6.1 for supportive care guidelines for MK-3475.

Table 3 Dose Modification Guidelines for Drug-Related Adverse Events

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Treatment Discontinuation
Diarrhea/Colitis	2-3	Toxicity resolves to Grade 0-1.	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue
AST, ALT, or Increased Bilirubin	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	3-4	Permanently discontinue (see exception below)[1]	Permanently discontinue
Type 1 diabetes mellitus (if new onset) or Hyperglycemia	T1DM or 3-4	Hold pembrolizumab for new onset Type 1 diabetes mellitus or Grade 3-4 hyperglycemia associated with evidence of beta cell failure.	Resume pembrolizumab when subjects are clinically and metabolically stable.
Hypophysitis	2-4	Toxicity resolves to Grade 0-1. Therapy with pembrolizumab can be continued while endocrine replacement therapy is instituted	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
Hyperthyroidism	3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue
Hypothyroidism		Therapy with pembrolizumab can be continued while thyroid replacement therapy is instituted	Therapy with pembrolizumab can be continued while thyroid replacement therapy is instituted.
Infusion Reaction	2[3]	Toxicity resolves to Grade 0–1	Permanently discontinue if toxicity develops despite adequate premedication
	3-4	Permanently discontinue	Permanently discontinue
Pneumonitis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	3-4 or Recurrent Grade 2	Permanently discontinue	Permanently discontinue
Renal Failure or Nephritis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	3-4	Permanently discontinue	Permanently discontinue
All Other Drug-Related Toxicity[2]	3 or Severe	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue

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

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

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

[3] If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate. Otherwise, dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose; Refer to Table 4 Infusion Reaction Treatment Guidelines for further management details.

Dosing interruptions are permitted in the case of medical/surgical events or logistical reasons not related to study therapy (e.g., elective surgery, unrelated medical events, subject vacation, and/or holidays). Subjects should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the subject's study record.

5.2.2 Timing of Dose Administration

MK-3475 should be administered on Day 1 of each cycle as a 30-minute IV infusion (25-40 min) every 3 weeks (Q3W) after all procedures/assessments have been completed as detailed on the Trial Flow Chart (Section 6.0), except for the post-infusion PK sample time points listed in the Trial Flow Chart. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. MK-3475 may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons only.

The specific time of trial treatment infusion (e.g., time of the week for first administration; time of the day for each administration) should take into consideration PK sampling time points and study visit procedures.

5.2.3 Trial Blinding/Masking

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

5.3 Randomization or Treatment Allocation

Subjects participating in this trial will be allocated by non-random assignment. Eligible subjects participating in this trial will be enrolled once a treatment number is assigned to the subject. Treatment allocation will occur centrally using an interactive voice response system (IVRS).

5.4 Stratification

No stratification based on age, sex or other characteristics will be used in this 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 any medication or vaccination specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The investigator should discuss any questions regarding this with the Sponsor Clinical Director. The final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary physician. However, the decision to continue the subject on trial therapy or vaccination schedule requires the mutual agreement of the investigator, the Sponsor and the subject.

5.5.1 Allowed 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 prior/concomitant medications received within 4 weeks 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:

- Antineoplastic systemic chemotherapy or biological therapy.
- Immunotherapy not specified in this protocol.
- Investigational agents other than MK-3475.
- Radiation therapy.
    - Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed after consultation with Sponsor.
- Live vaccines within 4 weeks 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 inactivated flu vaccines and are allowed.
- Glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology.
    - Note: The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.
- Generally, Traditional Chinese Medicine (TCM) is not recommend to use in this protocol, any usage of TCM should be discussed with sponsor's clinical director case by case.
    - Note: If the TCM have clear anti-tumor effect, or have similar pharmacology profile as prohibited concomitant medication listed in protocol, then it will not be allowed.
    - Note: Any TCM with unclear pharmacology profile or component will not be allowed (drug label should be provided for case by case discussion).
    - Note: Subject is not allowed to use Traditional Chinese medicine decoction without prescription.

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. Local surgery or radiation therapy (if indicated for palliative measure only after discussion with the SPONSOR) may be permitted beyond Week 24 tumor assessment.

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

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

5.6 Rescue Medications & Supportive Care

5.6.1 Supportive Care Guidelines for MK-3475

Adverse events (both non-serious and serious) associated with drug exposure and consistent with an immune phenomenon may represent an immunologic etiology. These immune related adverse events (irAEs) may be predicted based on the nature of the MK-3475. An irAE can occur shortly after the first dose or several months after the last dose of treatment. Particular attention should be paid to AEs that may be suggestive of potential irAEs as outlined below.

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

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

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

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

  - For Grade 3 or 4 diarrhea/colitis, treat with intravenous steroids followed by high dose oral steroids.
  - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

- Type 1 diabetes mellitus (if new onset, including diabetic ketoacidosis [DKA]) or ≥ Grade 3 Hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA)
  - For T1DM or Grade 3-4 Hyperglycemia
    - Insulin replacement therapy is recommended for Type I diabetes mellitus and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria.
    - Evaluate patients with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.

- Hypophysitis:
  - For Grade 2 events, treat with corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
  - For Grade 3-4 events, treat with an initial dose of IV corticosteroids followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

- Hyperthyroidism or Hypothyroidism:
  Thyroid disorders can occur at any time during treatment. Monitor patients for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders.
  - Grade 2 hyperthyroidism events (and Grade 2-4 hypothyroidism):
    - In hyperthyroidism, non-selective beta-blockers (e.g. propranolol) are suggested as initial therapy.
    - In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyroinine, is indicated per standard of care.
  - Grade 3-4 hyperthyroidism
    - Treat with an initial dose of IV corticosteroid followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
- Hepatic:
  - For Grade 2 events, monitor liver function tests more frequently until returned to baseline values (consider weekly).
    - Treat with IV or oral corticosteroids
  - For Grade 3-4 events, treat with intravenous corticosteroids for 24 to 48 hours.

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

- Renal Failure or Nephritis:
  - For Grade 2 events, treat with corticosteroids.
  - For Grade 3-4 events, treat with systemic corticosteroids.
  - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
- Management of Infusion Reactions: Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion.

Table 4 below shows treatment guidelines for subjects who experience an infusion reaction associated with administration of pembrolizumab (MK-3475).

Table 4 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 pembrolizumab (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. **Subject is permanently discontinued from further trial treatment administration.**	No subsequent dosing
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.		

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

Pembrolizumab may have adverse effects on a fetus in utero. Furthermore, it is not known if pembrolizumab has transient adverse effects on the composition of sperm.

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

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

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

OR

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

OR

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

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

(1) practice abstinence[†] from heterosexual activity;

OR

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

Acceptable methods of contraception are:

Single method (one of the following is acceptable):

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

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

- diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide)

- cervical cap with spermicide (nulliparous women only)
- contraceptive sponge (nulliparous women only)
- male condom or female condom (cannot be used together)
- hormonal contraceptive: oral contraceptive pill (estrogen/progestin pill or progestin-only pill), contraceptive skin patch, vaginal contraceptive ring, or subcutaneous contraceptive injection

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

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

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study subjects of childbearing potential must adhere to the contraception requirement (described above) from the day of study medication initiation (or 14 days prior to the initiation of study medication for oral contraception) throughout the study period up to 120 days after the last dose of trial therapy. If there is any question that a subject of childbearing potential 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 trial treatment. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the Sponsor 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 trial investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor. If a male subject impregnates his female partner the trial personnel at the site must be informed immediately and the pregnancy reported to the Sponsor and followed as described above and in Section 7.2.2.

5.7.4 Use in Nursing Women

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

5.8 Subject Withdrawal/Discontinuation Criteria

Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the investigator or the Sponsor if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding discontinuation or withdrawal procedures are provided in Section 7.1.4 – Other Procedures.

In this trial, a subject may discontinue from treatment but continue in the study in survival follow-up, as long as the subject does not withdraw consent. Once a subject has discontinued initial treatment, he/she may be eligible for retreatment if deemed medically appropriate and the subject meets the criteria, as outlined in Section 7.1.5.2.1
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.

Discontinuation of treatment does not represent withdrawal from the trial.

As certain data on clinical events beyond treatment discontinuation may be important to the study, they must be collected through the subject's last scheduled follow-up, even if the subject has discontinued treatment.

A subject must be discontinued from treatment (but may continue to be monitored in the trial) for any of the following reasons:

- The subject or legal representative (such as a parent or legal guardian) requests to discontinue treatment.
- Confirmed radiographic disease progression outlined in Section 7.1.5 (exception if the Sponsor approves treatment continuation).
- Unacceptable adverse experiences as described in Section 5.2.1.2
- Any progression or recurrence of any malignancy, or any occurrence of another malignancy that requires active treatment.Intercurrent illness other than another malignancy as noted above that prevents further administration of treatment
- Recurrent Grade 2 pneumonitis
- Completed 35 treatments (approximately 2 years) of MK-3475

  Note: 35 treatments (approximately 2 years) of study medication is calculated from the date of first dose. Subjects who stop MK-3475 after receiving 35 doses may be eligible for up to 17 cycles (1 year) additional study treatment if they progress after stopping study treatment provided they meet the requirements detailed in Section 7.1.5.2.1.
- 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
- Administrative reasons

The End of Treatment and Follow-up visit procedures are listed in Section 6.0 (Protocol Flow Chart) and Section 7.1.5 (Visit Requirements).

5.8.1 Temporary Discontinuation of Study Therapy after CR

Discontinuation of treatment may be considered for subjects who have attained an investigator-determined confirmed CR per RECIST 1.1 that have been treated for at least 8 cycles (24 weeks) with MK-3475 and had at least two treatments with MK-3475 beyond the date when the initial CR was declared.

Subjects who then experience radiographic disease progression per irRECIST may be eligible for up to 17 cycles (approximately 1 year) additional treatment with MK-3475 at the discretion of the investigator if no cancer treatment was administered since the last dose of MK-3475, the subject meets the safety parameters listed in the Inclusion/Exclusion criteria, and the trial is open. Subjects will resume therapy at the same dose and schedule at the time of initial discontinuation. Additional details are provided in Section 7.1.5.2.1.

5.9 Subject Replacement Strategy

A subject who discontinues from the trial will not be replaced.

5.10 Beginning and End of the Trial

The overall trial begins when the first subject signs the informed consent form. The overall trial ends when the last subject completes the last study-related phone-call or visit, discontinues from the trial or is lost to follow-up (i.e. the subject is unable to be contacted by the investigator).

5.11 Clinical Criteria for Early Trial Termination

The clinical trial may be terminated early if the extent (incidence and/or severity) of emerging effects/clinical endpoints is such that the risk/benefit ratio to the trial population as a whole is unacceptable. In addition, further recruitment in the trial or at (a) particular trial site(s) may be stopped due to insufficient compliance with the protocol, Good Clinical Practice (GCP) and/or other applicable regulatory requirements, procedure-related problems, or the number of discontinuations for administrative reasons is too high.

6.0 TRIAL FLOW CHART

6.1 Treatment Phase

Treatment Cycle (Week) / Title:	Screening	Treatment Cycles (2 mg/kg Q3W) [1]								End of Treatment	Post-Treatment		
	(-4)	1 (0)	2 (3)	3 (6)	4 (9)	5 (12)	6 (15)	7 (18)	8 (21) and beyond	Discon	Safety Follow-up	Follow Up Visits [2]	Survival Follow-Up [3]
Scheduling Window (Days):	-28		±3	±3	±3	±3	±3	±3	±3	At time of Discon	30 days (±3) post discon	Every 12 weeks (±7) post discon	
Administrative Procedures													
Informed Consent [4]	X												
Inclusion/Exclusion Criteria	X												
Subject Identification Card	X												
Demographics and Medical History	X												
Prior/Concomitant Medication Review [5]	X	X	X	X	X	X	X	X	X	X	X		
Trial Treatment Administration		X	X	X	X	X	X	X	X				
Post-study anticancer therapy status												X	
Survival Status													X
Clinical Procedures/Assessments													
Review Adverse Events [6]	X----------												----X
Full Physical Examination [7]	X					X			X				
Directed Physical Examination [7]		X	X	X	X		X	X		X			
Vital Signs, Height and Weight [8]	X	X	X	X	X	X	X	X	X	X			
12-Lead ECG	X												
ECOG Performance Status	X	X	X	X	X	X	X	X	X	X	X	X	
Laboratory Procedures/Assessments: analysis performed by local laboratory													
Pregnancy Test (Urine or Serum β-HCG) [9]	X												
Coagulation Parameters [10], [11]	X												
Hematology and Chemistry [11]	X		X	X	X	X	X	X	X	X	X [12]		
Urinalysis [11]	X						X			X	X [12]		
FT3, FT4 and TSH [11]	X			X		X		X		X	X [12]		
HIV, HBsAg, HCV-Ab, HCV-RNA	X												
Laboratory Procedures/Assessments: analysis performed by central laboratory													
Pharmacokinetics [13] [14]		X	X		X		X		X		X	X	
Anti-MK-3475 Antibodies [13]		X	X		X		X		X		X	X	

Treatment Cycle (Week) / Title:	Screening	Treatment Cycles (2 mg/kg Q3W) [1]								End of Treatment	Post-Treatment		
	(-4)	1 (0)	2 (3)	3 (6)	4 (9)	5 (12)	6 (15)	7 (18)	8 (21) and beyond	Discon	Safety Follow-up	Follow Up Visits [2]	Survival Follow-Up [3]
Scheduling Window (Days):	-28		±3	±3	±3	±3	±3	±3	±3	At time of Discon	30 days (±3) post discon	Every 12 weeks (±7) post discon	
Efficacy Measurements													
Tumor Imaging [15]	X					X		X	X			X	
Digital Photography (if applicable) [16]	X					X		X	X			X	
Tumor Tissue Collection [17]	X												
BRAF Testing [18]	X												

1) In general, assessments/procedures are to be performed on Day 1 and prior to the first dose of treatment for each cycle, and the window for each visit is ± 3 days unless otherwise specified. Treatment cycles are 3 weeks (Q3W).
2) In subjects who discontinue study therapy without documented disease progression, every effort should be made to continue post treatment follow up until (1) the start of new anti-cancer treatment, (2) documented disease progression, (3) death, or (4) the end of the study, whichever occurs first.
3) In subjects that experience documented disease progression or start a new anti-cancer therapy, contact should be made (e.g. by telephone) every 12weeks to assess for survival status. Additional survival follow-up contact between regularly performed calls may be performed based on pre-defined analyses in the protocol and/or for other data analyses purposes (for example, database locks)
4) Written consent must be obtained prior to performing any protocol specific procedure. Results of a test performed prior to the subject signing consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame (e.g., within 4 weeks prior to the first dose of trial treatment). Screening number will be assigned when the study informed consent is signed.
5) Prior medications – Record all medications taken within 4 weeks of screening visit. Concomitant medications – Enter new medications started during the trial through the Safety Follow-up visit. Record all medications taken for SAE/ECI s as defined in Section 7.2.
6) Record all AEs occurring within 30 days after the last dose of trial treatment. Report all SAEs occurring within 90 days after the last dose of trial treatment or 30 days of the end of treatment if the subject initiates new anticancer therapy, whichever is earlier. Report all ECIs occurring up until 30 days after the last dose of trial treatment or the start of new anti-cancer treatment, whichever comes first. Afterwards, report only SAEs and ECIs that are related to trial treatment. Adverse experiences and laboratory safety measurements will be graded per NCI CTCAE version 4.0. All adverse experiences, whether gradable by CTCAE or not, will also be evaluated for seriousness.
7) Perform physical examinations (PEs) at predose on the day of the study treatment visit. A full PE will be performed at screening and every 3 cycles after Cycle 5. Directed PEs will be performed at other visits where full PE is not performed.
8) Vital signs to include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at screening only.
9) For women of reproductive potential, a urine pregnancy test should be performed within 72 hours prior to first dose of trial treatment. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test performed by the local study site laboratory will be required. Pregnancy tests (serum and/or urine tests) should be repeated if required by local guidelines.
10) Coagulation factors (PT/INR and aPTT) should be tested as part of the screening procedures for all subjects. Any subject receiving anticoagulant therapy should have coagulation factors monitored closely throughout the trial.
11) Laboratory tests for screening are to be performed locally within 10 days prior to the first dose of trial treatment. After Cycle 1, lab samples can be collected up to 72 hours prior to the scheduled time point. Following Cycle 6, urinalysis should be performed every 6 cycles and FT3, FT4 and TSH should be performed every 2 cycles. See Section 7.1.3 for details regarding laboratory tests.
12) Unresolved abnormal labs that are drug related AEs should be followed until resolution or become non-clinically relevant. Labs do not need to be repeated after the end of treatment if labs are within normal range.
13) PK analysis will be performed in 30 subjects. Both PK and anti- MK-3475 antibody for subjects who receive MK-3475; Pre-dose trough PK and anti- MK-3475 antibody samples will be collected at Cycles 1, 2, 4, 6, 8 and every 4 cycles thereafter, 30 days after discontinuation of study drug, and 3 months after discontinuation of study drug (or until the subject starts new anti-cancer therapy). All pre-dose trough samples should be drawn within 24 hours before infusion of MK-3475.
14) Among 30 subjects, additional post-dose peak PK samples will be drawn within 30 minutes after end of MK-3475 infusion at Cycles 1 and 8. An additional single PK sample should be drawn at 24 hours (Day 2), between 72 and 168 hours (Day 4-8) and 336 hours (Day 15) after Cycle 1 dosing. Procedures for sample collection are described in the Procedures Manual.
15) The initial tumor imaging will be performed within 4 weeks prior to the first dose of trial treatment. Scans performed as part of routine clinical management are acceptable for use as the screening scan if they are of diagnostic quality and performed within 4 weeks prior to the first dose of trial treatment. Tumor imaging will be performed every 6 weeks (±7 day window) starting at Week 12 through Week 48. Following Week 48, tumor imaging may be performed approximately every 12 weeks (or whenever clinically indicated) while the patient remains on study therapy at the discretion of the investigator. Timing of imaging scans should follow the calendar and not be adjusted for treatment delays. Patients with an objective response or disease progression should have repeat imaging at least 4 weeks later to confirm the objective response or disease progression. CT scans are the required modality for measureable disease unless a patient has a clinical condition e.g. severe contrast allergy, or the lesions are significantly better visualized through the use of an MRI. The same imaging technique has to be used in a patient throughout the study. CTs should include the chest, abdomen, and pelvis. Pulmonary radiographic imaging for pneumonitis will be performed based on symptoms, the chest CT performed for tumor imaging may be used for pulmonary radiographic evaluation.

16) Qualitative digital photography should be performed at baseline and at time of scheduled tumor assessments for cutaneous lesions. Cutaneous lesions are not considered measurable for the purposes of this protocol, but may be considered to be non-target lesions for tumor assessments by investigators. Copies of digital photographs should also be submitted to the central imaging vendor.
17) Tumor tissue for biomarker analysis from an archival tissue sample or newly obtained biopsy (core or excisional: FNA/EBUS not adequate) of a tumor lesion not previously irradiated must be provided to the central vendor for characterization of PD-L1 status. Detailed instructions for tissue collection, processing and shipment are provided in the Procedures Manual.
18) BRAF V600 mutation analysis should be performed locally by the sites or at the central lab during screening in subjects without documented BRAF status.

6.2 Second Course Phase (Retreatment ONLY)

Treatment Cycle (Week) / Title:	Treatment Cycles (2 mg/kg Q3W) [1]								End of Treatment	Post-Treatment		
	1 (0)	2 (3)	3 (6)	4 (9)	5 (12)	6 (15)	7 (18)	8 (21) -17(48)	Discon	Safety Follow-up	Follow Up Visits [2]	Survival Follow-Up [3]
Scheduling Window (Days):		±3	±3	±3	±3	±3	±3	±3	At time of Discon	30 days (±3) post discon	Every 12 weeks (±7) post discon	
Administrative Procedures												
Eligibility Criteria (See Section 7.1.5.2.1)	X											
Concomitant Medication Review [4]	X	X	X	X	X	X	X	X	X	X		
Trial Treatment Administration	X	X	X	X	X	X	X	X				
Post-study anticancer therapy status											X	
Survival Status												X
Clinical Procedures/Assessments												
Review Adverse Events [5]	X---------- X											
Full Physical Examination [6]	X				X			X				
Directed Physical Examination [6]		X	X	X		X	X		X			
Vital Signs and Weight [7]	X	X	X	X	X	X	X	X	X			
12-Lead ECG	X											
ECOG Performance Status	X	X	X	X	X	X	X	X	X	X	X	
Laboratory Procedures/Assessments: analysis performed by local laboratory												
Pregnancy Test (Urine or Serum β-HCG) [8]	X											
Coagulation Parameters [9], [10]	X											
Hematology and Chemistry [10]	X	X	X	X	X	X	X	X	X	X [11]		
Urinalysis [10]	X					X			X	X [11]		
FT3, FT4 and TSH [10]	X		X		X		X		X	X [11]		
HIV, HBsAg, HCV-Ab, HCV-RNA	X											
Efficacy Measurements												
Tumor Imaging [12]	X				X		X	X			X	
Digital Photography (if applicable) [13]	X				X		X	X			X	

1) In general, assessments/procedures are to be performed on Day 1 and prior to the first dose of treatment for each cycle, and the window for each visit is ± 3 days unless otherwise specified. Treatment cycles are 3 weeks (Q3W).
2) In subjects who discontinue study therapy without documented disease progression, every effort should be made to conitnue post treatment follow up until (1) the start of new anti-cancer treatment, (2) documented disease progression, (3) death, or (4) the end of the study, whichever occurs first.
3) In subjects that experience documented disease progression or start a new anti-cancer therapy, contact should be made (e.g. by telephone) every 12weeks to assess for survival status. Additional survival follow-up contact between regularly performed calls may be performed based on pre-defined analyses in the protocol and/or for other data analyses purposes (for example, database locks)

4) Concomitant medications – Enter new medications started during the trial through the Safety Follow-up visit. Record all medications taken for SAE/ECI s as defined in Section 7.2.
5) Record all AEs occurring within 30 days after the last dose of trial treatment. Report all SAEs occurring within 90 days after the last dose of trial treatment or 30 days of the end of treatment if the subject initiates new anticancer therapy, whichever is earlier. Report all ECIs occurring up until 30 days after the last dose of trial treatment or the start of new anti-cancer treatment, whichever comes first. Afterwards, report only SAEs and ECIs that are related to trial treatment. Adverse experiences and laboratory safety measurements will be graded per NCI CTCAE version 4.0. All adverse experiences, whether gradable by CTCAE or not, will also be evaluated for seriousness.
6) Perform physical examinations (PEs) at predose on the day of the study treatment visit. A full PE will be performed at predose of the first dose of trial retreatment and every 3 cycles after Cycle 5. Directed PEs will be performed at other visits where full PE is not performed.
7) Vital signs to include temperature, pulse, respiratory rate, weight and blood pressure.
8) For women of reproductive potential, a urine pregnancy test should be performed within 72 hours prior to first dose of trial treatment. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test performed by the local study site laboratory will be required. Pregnancy tests (serum and/or urine tests) should be repeated if required by local guidelines.
9) Coagulation factors (PT/INR and aPTT) should be monitored closely throughout the trial for any subject receiving anticoagulant therapy. Any subject receiving anticoagulant therapy should have coagulation factors monitored closely throughout the trial.
10) Laboratory tests for determining eligibility for Second Course Phase are to be performed locally within 10 days prior to the first dose of trial retreatment. After Cycle 1, lab samples can be collected up to 72 hours prior to the scheduled time point. Following Cycle 6, urinalysis should be performed every 6 cycles and FT3, FT4 and TSH should be performed every 2 cycles. See Section 7.1.3 for details regarding laboratory tests.
11) Unresolved abnormal labs that are drug related AEs should be followed until resolution or become non-clinically relevant. Labs do not need to be repeated after the end of treatment if labs are within normal range.
12) The initial tumor imaging will be performed within 4 weeks prior to the first dose of trial treatment. Scans performed as part of routine clinical management are acceptable for use as the screening scan if they are of diagnostic quality and performed within 4 weeks prior to the first dose of trial treatment. Tumor imaging will be performed every 6 weeks (±7 day window) starting at Week 12 through Week 48. Following Week 48, tumor imaging may be performed approximately every 12 weeks (or whenever clinically indicated) while the patient remains on study therapy at the discretion of the investigator. Timing of imaging scans should follow the calendar and not be adjusted for treatment delays. Patients with an objective response or disease progression should have repeat imaging at least 4 weeks later to confirm the objective response or disease progression. CT scans are the required modality for measureable disease unless a patient has a clinical condition e.g. severe contrast allergy, or the lesions are significantly better visualized through the use of an MRI. The same imaging technique has to be used in a patient throughout the study. CTs should include the chest, abdomen, and pelvis. Pulmonary radiographic imaging for pneumonitis will be performed based on symptoms, the chest CT performed for tumor imaging may be used for pulmonary radiographic evaluation
13) Qualitative digital photography should be performed at baseline and at time of scheduled tumor assessments for cutaneous lesions. Cutaneous lesions are not considered measurable for the purposes of this protocol, but may be considered to be non-target lesions for tumor assessments by investigators. Copies of digital photographs should also be submitted to the central imaging vendor.

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 and or the Sponsor 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 or qualified designee must obtain documented consent from each potential subject or each subject's legally acceptable representative 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 IRB/ERC requirements, applicable laws and regulations and Sponsor requirements.

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 Subject Identification Card

All subjects will be given a Subject Identification Card identifying them as participants in a research trial. The card will contain trial site contact information (including direct telephone numbers) to be utilized in the event of an emergency. The investigator or qualified designee will provide the subject with a Subject Identification Card immediately after the subject provides written informed consent.

The subject identification card also contains contact information for the emergency unblinding call center so that a health care provider can obtain information about trial medication/vaccination in emergency situations where the investigator is not available.

7.1.1.4 Medical History

A medical history will be obtained by the investigator. 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. Record any prior cancer other than the current cancer evaluated in this study even if diagnosed greater than 10 years prior to the first dose of MK-3475. History of melanoma will be recorded separately and not listed as Medical History.

7.1.1.5 Prior and Concomitant Medications Review

7.1.1.5.1 Prior Medications

The investigator will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the subject within 4 weeks before starting the trial therapy. In addition, record all treatments for a prior cancer other than melanoma even if taken greater than 4 weeks prior to starting the trial therapy. Prior treatments for melanoma will be recorded separately and not listed as a prior medication.

7.1.1.5.2 Concomitant Medications

The investigator will record medication, if any, taken by the subject during the trial from start of study treatment through the 30-day safety follow-up visit. After the safety follow-up visit record all medications related to reportable SAEs and ECIs as defined in Section 7.2.

7.1.1.6 Disease Details and Treatments

7.1.1.6.1 Disease Details

The investigator will obtain prior and current melanoma disease details. BRAF status must be collected. If the site is unable to provide the documentation, then the Sponsor will offer this molecular testing of the tumor to be performed locally by the sites or at the central lab during screening. NRAS and c-KIT status will also be collected if available. Detailed

instructions for tissue collection, processing and shipment are provided in the Procedure Manual.

7.1.1.6.2 Prior Treatment Details

The investigator will review all prior cancer treatments for melanoma including systemic treatments, radiation and surgeries.

7.1.1.6.3 Subsequent Antineoplastic Therapy Status

The investigator will review all new anti-neoplastic therapy initiated after the last dose of trial treatment. If a subject initiates a new anti-neoplastic 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-neoplastic therapy has been initiated the subject will move into survival follow-up.

7.1.1.7 Assignment of Screening Number

All consented subjects will be given a unique screening number that will be used to identify the subject for all procedures that occur prior to randomization or treatment allocation. Each subject will be assigned only one screening number. Screening numbers must not be re-used for different subjects.

Any subject who is screened multiple times will retain the original screening number assigned at the initial screening visit.

Specific details on the screening visit requirements (screening/rescreening) are provided in Section 7.1.5.1.

7.1.1.8 Assignment of Treatment/Randomization Number

All eligible subjects will be allocated, by non-random assignment, and will receive a treatment/randomization number. The treatment/randomization number identifies the subject for all procedures occurring after treatment allocation/randomization. Once a treatment/randomization number is assigned to a subject, it can never be re-assigned to another subject.

A single subject cannot be assigned more than 1 treatment/randomization number.

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

Interruptions from the protocol specified treatment plan for greater than 12 weeks between MK-3475 doses due to toxicity require require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on subject management.

Administration of trial medication will be witnessed by the investigator and/or trial staff. The total volume of trial treatment infused will be compared to the total volume prepared to determine compliance with each dose administered. The instructions for preparing and administering MK-3475 will be provided in the Procedures Manual.

7.1.2 Clinical Procedures/Assessments

7.1.2.1 Adverse Event (AE) Monitoring

The investigator 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 Appendix 12.5). 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 a potentially immunologic etiology (irAE). See Section 5.6.1 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 Physical Exam

The investigator will perform a full physical exam during the screening period. Clinically significant abnormal findings should be recorded as medical history. A full physical exam should be performed as specified in the Trial Flow Chart (Section 6.0). For cycles that do not require a full physical exam per the Trial Flow Chart, the investigator will perform a directed physical exam as clinically indicated prior to trial treatment administration. After the first dose of trial treatment new clinically significant abnormal findings should be recorded as AEs.

7.1.2.3 Vital Signs, Height and Weight

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.

Subjects must be resting in a sitting position for approximately 10 minutes prior to obtaining vital signs. Height will be measured at screening only.

If blood pressure is >150/100 mmHg in a subject without a history of hypertension, or increased >20 mmHg (diastolic) from baseline measurement in a subject with a previous history of hypertension, the assessment should be repeated in 10 minutes for confirmation.

7.1.2.4 12-lead Electrocardiogram (ECG)

A standard 12-lead ECG will be performed using local standard procedures once at screening. Clinically significant abnormal findings should be recorded as medical history. Additional time points may be performed as clinically necessary.

7.1.2.5 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status (see Section 12.4) as specified in the Trial Flow Chart.

7.1.2.6 Tumor Imaging and Assessment of Disease

Processes for image collection and transmission to the central vendor can be found in the Procedure Manual. The Site Imaging Manual will provide details on acquisition parameters and image transmission practices required for this trial.

7.1.2.6.1 Initial Tumor Imaging

To meet screen criteria, initial tumor imaging must be performed within 4 weeks prior to treatmen. This scan will be considered the baseline assessment for the study. Central imaging vendor must review screening images to confirm the subject has at least one target lesion per standard RECIST 1.1.

Scans performed as part of routine clinical management are acceptable for use as the baseline scan if they are of diagnostic quality and performed within 4 weeks prior to randomization.

7.1.2.6.2 Tumor Imaging During Trial

The first on-study imaging assessment should be performed at 12 weeks from the date of first dose of MK-3475. Subsequent imaging should be performed every 6 weeks (± 7 days) starting at 12 weeks through 48 weeks. After Week 48, the frequency of imaging will be every 12 weeks (± 7 days). Imaging may be more frequent if clinically indicated. Imaging should not be delayed for delays in cycle starts.

Note: *The exact same image acquisition and processing parameters should be used throughout the study*.

Per RECIST 1.1, response should be confirmed by a repeat radiographic assessment not less than 4 weeks from the date the response was first documented. The scan for confirmation of response may be performed at the earliest 4 weeks after the first indication of response, or at the next scheduled scan (i.e. 6 weeks later), whichever is clinically indicated. Subjects will then return to regular scheduled imaging, starting with the next scheduled imaging time point. Subjects who obtain a confirmation scan do not need to undergo the next scheduled tumor imaging if it is < 4 weeks later; tumor imaging may resume at the subsequent scheduled imaging time point.

At the time of the initial PD by RECIST 1.1 imaging scans should be sent to central vendor to verify progressive disease. If PD is verified, the investigator may choose to continue treatment if the patient is clinically stable and repeat imaging in 4 weeks to confirm PD (by the site) by irRECIST. Imaging should continue to be performed until documented disease progression, the start of new anti-cancer treatment, withdrawal of consent, death, or the end of the trial, whichever occurs first. For subjects receiving MK-3475 per irRECIST disease progression should be confirmed at least 4 weeks after the first scan indicating PD in clinically stable subjects. Subjects who have unconfirmed disease progression may continue

on treatment until progression is confirmed provided they have met the conditions detailed in Section 7.1.2.6.2.

In clinically stable subjects, disease progression may be confirmed by the site at least 4 weeks after the first scan indicating PD.

7.1.2.6.3 Assessment of Disease

Standard RECIST 1.1 will be applied by the central imaging vendor as the primary measure for assessment of tumor response, date of disease progression, and as a basis for all protocol guidelines related to disease status. Scans showing site-assessed PD should be submitted to the central imaging vendor immediately. The site will be notified when the imaging vendor verifies disease progression using RECIST 1.1..

7.1.2.6.4 Immune-related RECIST (irRECIST)

Following PD by RECIST 1.1, sites will assess tumor response and progression per immune-related RECIST (irRECIST) for subjects receiving MK-3475 as this data will be collected in the clinical database. Tumor imaging should also be submitted to central imaging vendor for assessment of tumor response per irRECIST as this data will be collected in clinical database as well.

irRECIST is RECIST 1.1 adapted for use with immunotherapies as described in the Procedure Manual and irRECIST Tip Sheet.

If imaging shows progressive disease (PD), tumor assessment may be repeated by the site at least 4 weeks later in order to confirm PD with the option of continuing treatment until this scan is obtained for clinically stable subjects (see Table 5). Figure 2 illustrates the imaging flow involving verification of PD for clinically stable subjects. Clinically stable is defined by the following criteria:

- Absence of signs and symptoms indicating disease progression
- No decline in ECOG performance status
- Absence of rapid progression of disease
- Absence of progressive tumor at critical anatomical sites (e.g., cord compression) requiring urgent alternative medical intervention

Table 5 Imaging and Treatment after 1st Radiologic Evidence of Progressive Disease (PD)

	Clinically Stable		Clinically Unstable	
	Imaging	**Treatment**	**Imaging**	**Treatment**
1st radiologic evidence of PD by RECIST 1.1 which has been verified by the central imaging vendor	Repeat imaging at ≥ 4 weeks to confirm PD	May continue study treatment at the Investigator's discretion while awaiting confirmatory scan by site by irRECIST	Repeat imaging at ≥ 4 weeks to confirm PD per physician discretion only	Discontinue treatment
Repeat scan confirms PD by irRECIST at the local site	No additional imaging required	Discontinue treatment (exception is possible upon consultation with Sponsor).	No additional imaging required	N/A
Repeat scan shows SD, PR or CR by RECIST1.1 at the local site	Continue regularly scheduled imaging assessments every 6 weeks (every 12 weeks after 48 weeks)	Continue study treatment at the Investigator's discretion	Continue regularly scheduled imaging assessments every 6 weeks (every 12 weeks after 48 weeks)	May restart study treatment if condition has improved and/or clinically stable per Investigator's discretion.

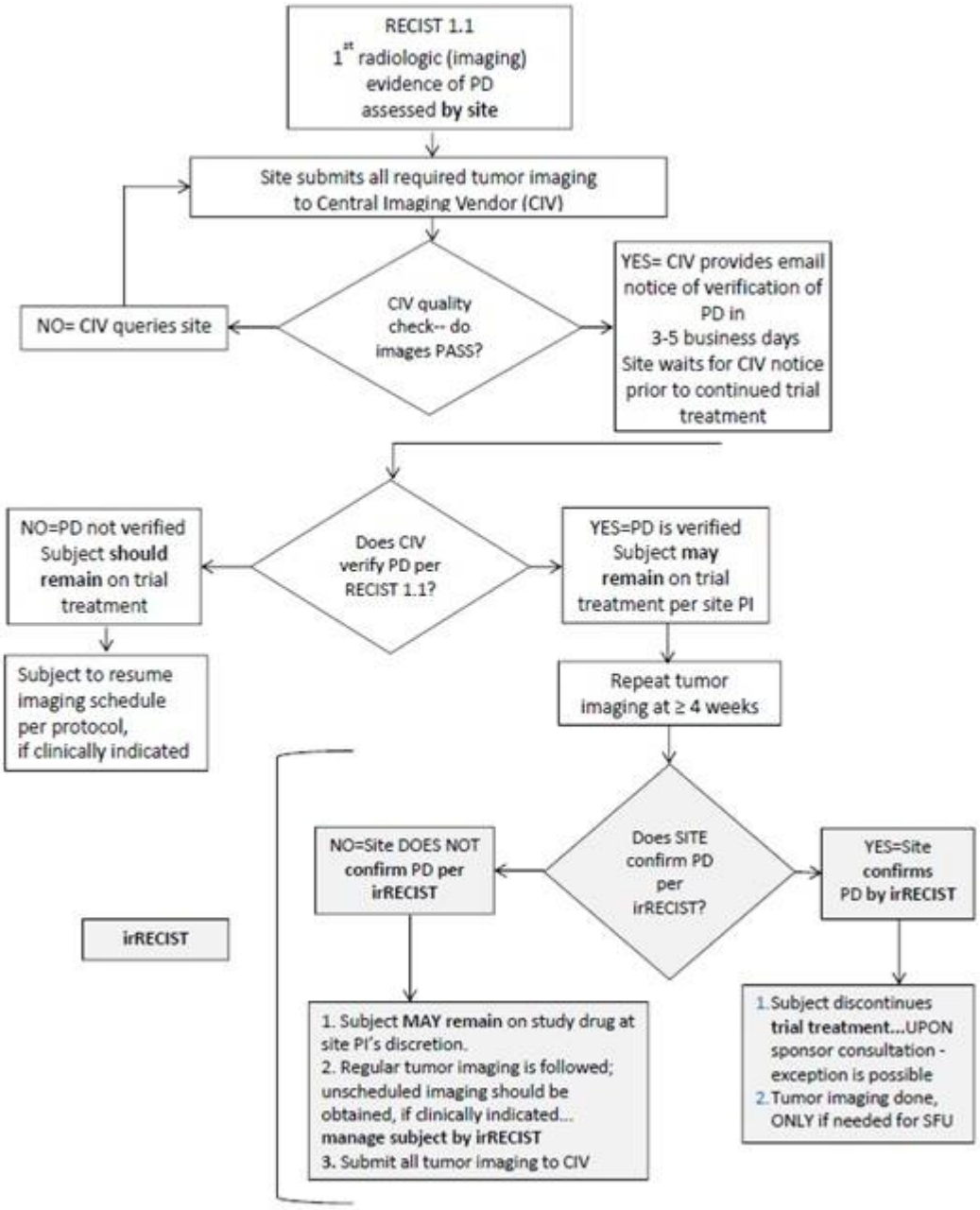

Figure 2 Imaging and Treatment for Clinically Stable Subjects after First Radiologic Evidence of PD Assessed by the Site

In determining whether or not the tumor burden has increased or decreased, investigators should consider all target lesions as well as non-target lesions (please refer to the irRECIST Tip Sheet). Subjects that are deemed clinically unstable are not required to have repeat imaging for confirmation. If radiologic progression is confirmed, it is recommended that the subject be discontinued from trial treatment unless, in the investigator's opinion, the subject is deriving benefit from treatment. Clinically stable subjects as defined above may continue to receive trial therapy after discussion with the Sponsor.

If a subject has unconfirmed progression of disease and is clinically stable, it is at the discretion of the investigator to continue treating the subject with the assigned treatment per protocol until progression of disease is confirmed at least 28 days from the date of the scan suggesting progression of disease. If progression is not confirmed on the subsequent scan, the subject should continue to receive study therapy and radiographic scans obtained to monitor for disease status every 6 weeks (± 7 days) starting at 12 weeks through 48 weeks, or every 12 weeks (± 7 days) after week 48.

The same imaging technique, acquisition, and processing parameters should be used in a subject throughout the trial. Details are provided in the Site Imaging Manual.

NOTE: In subjects who discontinue study therapy without documented disease progression, every effort should be made to continue monitoring their disease status by radiologic imaging every 12 weeks (± 7 days) until (1) the start of new anti-cancer treatment, (2) disease progression (3) death, or (4) the end of the study, whichever occurs first. See the Trial Flow Charts in Section 6.0 and Section 7.1.5.3 for information about the Follow-up Visits.

7.1.2.7 Photography for Cutaneous Lesions

Digital photographs documenting measureable cutaneous lesions should be obtained if the cutaneous lesion is included as part of the non-target lesions for disease assessment according to RECIST 1.1. Copies of the photograph should be forwarded to the central vendor for potential retrospective analysis. The timing for capturing cutaneous lesion photographs should follow the same schedule as the imaging scans. The requirement for the digital photographs and the process for transmitting photographs to the central vendor is located in the Procedures Manual.

7.1.2.8 Tumor Tissue Collection

Participation in this trial will require submitting tumor sample from a newly obtained formalin-fixed specimen from locations not radiated prior to biopsy; no new systemic antineoplastic therapy may be administered between the PD-L1 biopsy and initiating study medication. The specimen will be evaluated at a central laboratory facility for expression status of PD-L1 by IHC in a retrospective manner. Both PD-L1 positive and negative subjects as determined by the central laboratory facility will be enrolled in this trial. Newly-obtained specimens are defined as formalin-fixed paraffin embedded (FFPE)-preserved blocks of tissue collected at screening.

Note: A fine needle aspirate (FNA) or cytologic specimen will not be acceptable. Core needle or excisional biopsies, or resected tissue is required.

Site must be able to provide documentation of the subject's tumor BRAF mutation status. BRAF V600 testing can be performed locally by the sites or at the central lab during screening, if not already known when the subject signs informed consent.

If the subject signs the FBR consent, any leftover tissue that would ordinarily be discarded at the end of the main study will be retained for FBR. Details regarding time points for collection of tumor tissue are outlined in the Study Flow Chart – Section 6.1.

Detailed instructions for tissue collection, processing and shipment are provided in the Procedures Manual

7.1.3 Laboratory Procedures/Assessments

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

7.1.3.1 Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

Laboratory tests for hematology, chemistry and urinalysis are specified in Table 6.

Table 6 Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Blood	Serum β-human chorionic gonadotropin (β-hCG) *
Hemoglobin	Alkaline phosphatase	Glucose	PT (INR)
Platelet count	Alanine aminotransferase (ALT)	Protein	aPTT
WBC (total and differential)	Aspartate aminotransferase (AST)	Specific gravity	Free triiodothyronine (FT3)
Red Blood Cell Count	Lactate dehydrogenase (LDH)	Microscopic exam, if abnormal results are noted	Free thyroxine (FT4)
Absolute Neutrophil Count	Creatinine	Urine pregnancy test*	Thyroid stimulating hormone (TSH)
Absolute Lymphocyte Count	Uric Acid		HIV antibody**
	Calcium		HBsAg**
	Chloride		HCV Ab**
	Glucose		HCV RNA**
	Phosphorus		IgG
	Potassium		
	Sodium		
	Magnesium		
	Total Bilirubin		
	Direct Bilirubin, if total bilirubin is elevated above the upper limit of normal		
	Total protein		
	Blood Urea Nitrogen or Urea		

* Perform on women of childbearing potential only. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required.
** For screening visit only.

Laboratory tests (hematology, serum chemistry, urinalysis, coagulation parameters, thyroid function) for screening or entry into the Second Course Phase 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 and found to be acceptable prior to each dose of trial treatment.

PT/INR and aPTT will be collected as coagulation parameters.

TSH, FT3, and FT4 will be measured for thyroid function test.

Testing for HIV 1/2 antibodies, HBsAg, and HCV-Ab, HCV RNA (qualitative) will be performed at screening. If results of these tests obtained within 3 months before screening are available, they can be used even before consent is obtained.

For women of reproductive potential, a urine/serum pregnancy test will be performed within 72 hours of the first dose. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required.

7.1.3.2 Pharmacokinetic/ Immunogenicity Evaluations

To further evaluate MK-3475 immunogenicity and MK-3475 exposure in this indication, and also to evaluate exposure of the proposed dosing regimen, sample collections for analysis of anti-drug antibodies (ADA) and PK are currently planned as shown in the Trial Flow Chart . Blood samples will be obtained to measure pharmacokinetics of serum MK-3475 as monotherapy. The MK-3475 serum maximum concentration (C_{max}) and minimum concentration (C_{trough}) at planned visits and times will be summarized. If ongoing ADA and/or PK results continue to be consistent with existing ADA and/or PK data from other MK-3475 clinical trials, it may be decided to discontinue or reduce further sample collection in this study.

Pharmacokinetic data will also be analyzed using nonlinear mixed effects modeling. Based on pharmacokinetic (PK) data obtained in this study as well as PK data obtained from other studies (if available), a population PK analysis will be performed to characterize pharmacokinetic parameters (Clearance (CL), Volume of distribution (V)) and to evaluate the effect of extrinsic and intrinsic factors to support proposed dosing regimen. Pharmacokinetic data will also be used to explore the exposure-response relationships for MK-3475 antitumor activity/efficacy as well as safety in the proposed patient population, if feasible. The results of these analyses, if performed, will be reported separately.

7.1.3.2.1 Blood Collection for Serum MK-3475

The time points for PK blood sampling are described in Section 6 – Trial Flow Chart. Sample collection, storage and shipment instructions for the serum samples will be provided in the Procedures Manual. PK samples should be drawn according to the PK collection schedule for subjects who receive MK-3475. Every effort should be taken to collect samples at 30 days and 3 months after end of MK-3475 treatment or until start of a new anti-cancer therapy, whichever occurs first.

7.1.3.2.2 Blood Collection for Serum Anti-MK-3475 Antibodies

The time points for Anti-MK-3475 Antibodies blood sampling are described in Section 6 – Trial Flow Chart. Sample collection, storage and shipment instructions for the serum samples will be provided in the Procedures Manual. Anti-MK-3475 antibody samples should be drawn according to the ADA collection schedule for subjects who receive MK-3475. Every effort should be taken to collect samples at 30 days and 3 months after end of MK-

3475 treatment for ADA. Simultaneous PK sampling is required for interpretation of ADA analysis or until start of a new anti-cancer therapy, whichever occurs first.

7.1.4 Other Procedures

7.1.4.1 Withdrawal/Discontinuation

When a subject discontinues/withdraws from participation in the trial, 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.

7.1.4.2 Blinding/Unblinding

This is an open label trial; there is no blinding for this trial.

7.1.4.3 Calibration of Critical Equipment

The investigator or qualified designee has the responsibility to ensure that any critical device or instrument used for a clinical evaluation/test during a clinical trial that provides important information about inclusion/exclusion criteria and/or safety or efficacy parameters shall be suitably calibrated and maintained to ensure that the data obtained is reliable and/or reproducible. Documentation of equipment calibration must be retained as source documentation at the trial site.

Critical Equipment for this trial includes:

- Laboratory equipment – as required for inclusion labs and trial assessments.
- Imaging equipment – as required for study objectives.

See protocol-specified guidance in the Administrative Binder, Procedures Manual, Site Imaging Manual (SIM) and irRECIST Tip Sheet.

7.1.5 Visit Requirements

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

7.1.5.1 Screening

Up to 4 weeks prior to enrollment, potential subjects will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5.1. Visit requirements are outlined in Section 6.0 – Trial Flow Chart.

Written consent for the study must be obtained prior to performing any protocol specific procedure. After providing consent, subjects will be assigned a screening number. Results of a test performed prior to the subject signing consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame. Screening procedures are to be completed within 4 weeks prior to the first dose of trial treatment except for the following:

- Laboratory tests (hematology, serum chemistry, urinalysis, coagulation parameters, thyroid function test) are to be performed within 10 days prior to the first dose of trial treatment.
- For women of reproductive potential, a urine pregnancy test will be performed within 72 hours prior to the first dose of trial treatment. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required (performed by the local study site laboratory).
- If results of HIV 1/2 antibodies, HBsAg, and HCV-Ab, HCV-RNA (qualitative) test obtained within 3 months before screening are available, they can be used even before consent is obtained.
- Archival tumor biopsy for PD-L1 characterization is not required to be obtained within 4 weeks prior to the first dose of trial treatment.

Subjects may be rescreened after initially failing to meet the inclusion/exclusion criteria. Results from assessments performed during the initial screening period are acceptable in lieu of a repeat screening test if performed within the specified time frame and the inclusion/exclusion criteria is met.

7.1.5.2 Treatment Period

Visit requirements are outlined in Section 6.0 - Trial Flow Chart. Specific procedure-related details are provided above in Section 7.1 - Trial Procedures. Subject will be received study treatment until the subject meets 5.8 Discontinuation criteria.

7.1.5.2.1 Second Course Phase (Retreatment Period)

Subjects who stop MK-3475 with SD or better may be eligible for up to 17 additional cycles (approximately 1 year) of pembrolizumab (MK-3475) treatment if they progress after stopping trial treatment from the initial treatment phase and with SPONSOR approval. This retreatment is termed the Second Course Phase of this study and is only available if the study remains open and the subject meets the following conditions:

- Either
    - Stopped initial treatment with MK-3475 after attaining an investigator-determined confirmed CR according to RECIST 1.1.
        - Was treated for at least 8 cycles with MK-3475 before discontinuing therapy.
        - Received at least two treatments with MK-3475 beyond the date when the initial CR was declared.

  OR
    - Subject had SD, PR or CR and stopped MK-3475 treatment after 35 administrations (approximately 2 years) of trial treatment for reasons other than disease progression or intolerability.

AND

- Experienced an investigator-determined confirmed radiographic disease progression after stopping their initial treatment with MK-3475. A scan documenting PD should be performed within 4 weeks prior to starting Second Course treatment.
- Did not receive any anti-cancer treatment since the last dose of MK-3475.

- Have a performance status of 0 or 1 on the ECOG Performance Scale.
- Demonstrate adequate organ function as detailed in Section 5.1.2.
- Female subject of childbearing potential should have a negative urine or serum pregnancy test within 72 hours prior to receiving retreatment with study medication.
- 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 child bearing potential are those who have not been surgically sterilized or have not been free from menses for > 1 year.
- 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.
- Does not have a history or current evidence of any condition, therapy, or laboratory abnormality that might 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.

Subjects who restart treatment will be retreated at the same dose frequency as when they last received MK-3475. Treatment will be administered for up to 17 additional cycles (approximately 1 year) of pembrolizumab (MK-3475) treatment. Visit requirements are outlined in Section 6.0 – Trial Flow Chart.

7.1.5.3 Discontinuation

When a subject discontinues trial treatment in treatment period and/or retreatment period, procedures for discontinuation will be conducted.

7.1.5.4 Post-Treatment Visits

7.1.5.4.1 Safety Follow-Up Visit

The mandatory Safety Follow-Up Visit should be conducted approximately 30 days after the last dose of trial treatment or before the initiation of a new anti-neoplastic 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 baseline until the beginning of a new anti-neoplastic therapy, whichever occurs first. SAEs that occur within 90 days of the end of treatment or 30 days of the end of treatment if the subject initiates new anticancer therapy, whichever is earlier, should also be followed and recorded.

Subjects who are eligible for retreatment with MK-3475 (as described in Section 7.1.5.2.1) may have up to two safety follow-up visits, one after the Treatment Period and one after the Second Course Phase.

7.1.5.4.2 Follow-up Visits

Subjects who discontinue trial treatment for a reason other than disease progression will move into the Follow-Up Phase and should be assessed every 12 weeks (± 1 week) by radiologic imaging to monitor disease status and collect serum samples for pharmacokinetics

and anti-MK-3475 antibodies as specified in the Trial Flow Chart (Section 6.0). Every effort should be made to collect information regarding disease status and serum samples until the start of new anti-neoplastic therapy, disease progression, withdrawal of consent, death, or the end of the study, whichever occurs first. Information regarding post-study anti-neoplastic treatment will be collected if new treatment is initiated.

Subjects who are eligible to receive retreatment with MK-3475 according to the criteria in Section 7.1.5.2.1 will move from the follow-up phase to the Second Course Phase when they experience disease progression. Details are provided in Section 6.2 – Trial Flow Chart for Retreatment.

7.1.5.4.3 Survival Follow-up

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

7.2 Assessing and Recording Adverse Events

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavourable 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 Sponsor'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.

Sponsor's 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 the Sponsor for human use.

Adverse events may occur during clinical trials, or as prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

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

All adverse events that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but

not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

From the time of treatment allocation/randomization through 30 days following cessation of treatment, all adverse events must be reported by the investigator. Such events will be recorded 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. The investigator will make every attempt to follow all subjects with non-serious adverse events for outcome.

Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

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

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

For purposes of this trial, an overdose will be defined as any dose exceeding the prescribed dose for ≥1000 mg of pembrolizumab. No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, study treatment 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 Sponsor's product or vaccine, the adverse event(s) is reported as a serious adverse event, even if no other seriousness criteria are met.

If a dose of Sponsor's product or vaccine 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 by the investigator within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

7.2.2 Reporting of Pregnancy and Lactation to the Sponsor

Although pregnancy and lactation are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them) that occurs during the trial.

Pregnancies and lactations that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but

not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

Pregnancies and lactations that occur from the time of treatment allocation/randomization through 120 days following cessation of Sponsor's product, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, must be reported by the investigator. All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Such events must be reported within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

7.2.3 Immediate Reporting of Adverse Events to the Sponsor

7.2.3.1 Serious Adverse Events

A serious adverse event is any adverse event occurring at any dose or during any use of Sponsor'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 an other important medical event.

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

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

Refer to Table 7 for additional details regarding each of the above criteria.

For the time period beginning when the consent form is signed until treatment allocation/randomization, any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study (reference Section 7.2.3.3 for additional details), that occurs to any subject must be reported within 24 hours to the Sponsor if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the

cancer under study (reference Section 7.2.3.3 for additional details), whether or not related to the Sponsor's product, must be reported within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent)

Additionally, any serious adverse event, considered by an investigator who is a qualified physician to be related to the Sponsor's product that is brought to the attention of the investigator at any time following consent through the end of the specified safety follow-up period specified in the paragraph above, or at any time outside of the time period specified in the previous paragraph also must be reported immediately to the Sponsor.

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 reported to the Sponsor.

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

For the time period beginning at treatment allocation/randomization through 30 days following cessation of treatment, any ECI, or follow up to an ECI, whether or not related to the Sponsor’s product, must be reported within 24 hours to the Sponsor, either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

Events of clinical interest for this trial include:

1. an overdose of Sponsor's product, as defined in Section 7.2.1 - Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor, that is not associated with clinical symptoms or abnormal laboratory results.
2. an elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

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

7.2.3.3 Protocol-Specific Exceptions to Serious Adverse Event Reporting

Efficacy endpoints as outlined in this section will not be reported to the Sponsor as described in Section 7.2.3.

Specifically, the suspected/actual events covered in this exception include any event that is disease progression of the cancer under study.

The Sponsor will monitor unblinded aggregated efficacy endpoint events and safety data to ensure the safety of the subjects in the trial. Any suspected endpoint which upon review is not progression of the cancer under study will be forwarded to global safety as a SAE within 24 hours of determination that the event is not progression of the cancer under study.

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 7 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 Sponsor's 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 for an elective procedure to treat a pre-existing condition that has not worsened is not a serious adverse event. A pre-existing condition is a clinical condition that is diagnosed prior to the use of a Merck product and is documented in the patient's medical history.); 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) **(**although not serious per ICH definition, is reportable to the Sponsor within 24 hours to meet certain local requirements); **or**	
	Is an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event for collection purposes. 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 Sponsor's product to be discontinued?	
Relationship to Sponsor's Product	Did the Sponsor's product cause the adverse event? The determination of the likelihood that the Sponsor's 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 Sponsor's product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Sponsor's product caused the adverse event (AE):	
	Exposure	Is there evidence that the subject was actually exposed to the Sponsor's 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 Sponsor's 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 Sponsor's Product (continued)	**The following components are to be used to assess the relationship between the test drug and the AE: (continued)**	
	Dechallenge	Was the Sponsor's 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 Sponsor's product; or (3) the trial is a single-dose drug trial); or (4) Sponsor's product(s) is/are only used one time.)
	Rechallenge	Was the subject re-exposed to the Sponsor's 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) Sponsor's 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 SPONSOR'S PRODUCT, OR IF REEXPOSURE TO THE SPONSOR'S PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE SUBJECT, THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR CLINICAL DIRECTOR 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 Sponsor's 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 Sponsor's product relationship).**	
Yes, there is a reasonable possibility of Sponsor's product relationship.	There is evidence of exposure to the Sponsor's product. The temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable. The AE is more likely explained by the Sponsor's product than by another cause.	
No, there is not a reasonable possibility of Sponsor's product relationship	Subject did not receive the Sponsor's product OR temporal sequence of the AE onset relative to administration of the Sponsor's product is not reasonable OR the AE is more likely explained by another cause than the Sponsor's product. (Also entered for a subject with overdose without an associated AE.)	

7.2.5 Sponsor Responsibility for Reporting Adverse Events

All Adverse Events will be reported to regulatory authorities, IRB/IECs and investigators in accordance with all applicable global laws and regulations, i.e., per ICH Topic E6 (R1) Guidelines for Good Clinical Practice.

8.0 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, but prior to any final database lock, changes made to primary and/or key secondary hypotheses, or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with ICH Guideline E-9). Changes to exploratory or other non-confirmatory analyses made after the protocol has been finalized, but prior to final database lock, will be documented in a supplemental SAP (sSAP) and referenced in the Clinical Study Report (CSR) for the study. Post hoc exploratory analyses will be clearly identified in the CSR.

8.1 Statistical Analysis Plan Summary

Key elements of the statistical analysis plan are summarized below; the comprehensive plan is provided in Sections 8.2-8.12.

Study Design Overview	**Phase Ib Study of MK-3475 in Chinese Subjects with Advanced Melanoma**
Treatment Assignment	MK-3475 2 mg/kg every 3 weeks (Q3W)
Analysis Populations	Efficacy: Full Analysis Set (FAS) Safety: All Subjects as Treated (ASaT)
Primary Endpoint(s)	ORR based on RECIST 1.1 assessed by the central independent radiology review
Statistical Methods for Key Efficacy Analyses	The primary hypothesis will be evaluated by providing the point estimate, 95% confidence interval, and p-value for testing the centrally reviewed RECIST 1.1 ORR is greater than the historical control (10%). The ORR will be estimated using exact binomial distribution.
Statistical Methods for Key Safety Analyses	Summary statistics (counts, percentage, mean, standard deviation, etc.) will be provided for the safety endpoints as appropriate.
Interim Analyses	No interim analyses are planned in this trial.
Multiplicity	No multiplicity adjustment is planned.
Sample Size and Power	The planned sample size is 80 subjects. For the ORR per RECIST 1.1 assessed by the central independent radiology review, the trial has 90% power to demonstrate that MK-3475 is better than historical control (10%) at an overall one-sided 2.5% alpha-level, if the underlying RECIST 1.1 ORR per central independent radiology review of MK-3475 is 24%.

8.2 Responsibility for Analyses/In-house Blinding

The statistical analysis of the data obtained from this study will be the responsibility of the Clinical Biostatistics department of the SPONSOR.

This trial is being conducted as an open-label study, i.e., subjects, investigators, and SPONSOR personnel will be aware of subject treatment assignments after each subject is enrolled and treatment is assigned.

The Sponsor will generate the treatment numbers for this protocol, and the assignment of treatment number will be implemented in IVRS (see section 7.1.1.8).

8.3 Hypotheses/Estimation

Objectives and hypotheses of the study are stated in Section 3.0.

8.4 Analysis Endpoints

8.4.1 Efficacy Endpoints

Primary Efficacy Endpoint

- Overall response rate (ORR) per RECIST 1.1 assessed by the central independent radiology review

The ORR is defined as the proportion of subjects in the analysis population who have complete response (CR) or partial response (PR) using RECIST 1.1 criteria at any time during the study. Response for the primary analysis will be determined by the central independent radiology review.

Secondary Efficacy Endpoints

- Duration of Response (DOR) - per RECIST 1.1 and per irRECIST assessed by the central independent radiology review: For subjects who demonstrated CR or PR, response duration is defined as the time from first documented evidence of CR or PR until disease progression or death. Subjects died without documented disease progression would be counted as event (PD) at the last non-PD assessment. Response duration for subjects who have not progressed or died at the time of analysis will be censored at the date of their last tumor assessment.

- Progression-free Survival (PFS) - per RECIST 1.1 and per irRECIST assessed by the central independent radiology review: PFS is defined as the time from randomization to the first documented disease progression or death due to any cause, whichever occurs first

- Overall response rate (ORR) per irRECIST assessed by the central independent radiology review

- Overall survival (OS): is defined as the time from randomization to death due to any cause. Subjects without documented death at the time of the final analysis will be censored at the date of the last follow-up

8.4.2 Safety Endpoints

A description of safety measures is provided in Section 7.0.

8.5 Analysis Populations

8.5.1 Efficacy Analysis Populations

The Full Analysis Set (FAS) population will serve as the population for the analysis of ORR, PFS, and OS in this study. The FAS population consists of all allocated subjects with subjects excluded for the following reasons:

- Failure to receive at least one dose of study treatment,
- Lack of baseline data for those analyses that require baseline data

The efficacy analysis will be conducted at the time when all subjects are enrolled and have either discontinued/ have progression disease or have at least 24 weeks of follow-up since first dose of last enrolled subjects, whichever occurs first.

The analysis population for DOR consists of responders

Details on the approach to handling missing data are provided in Section 8.6 Statistical Methods.

8.5.2 Safety Analysis Populations

The All Subjects as Treated (ASaT) population will be used for the analysis of safety data in this study. The ASaT population consists of all allocated subjects who received at least one dose of study treatment.

At least one laboratory or vital sign measurement obtained subsequent to at least one dose of study treatment is required for inclusion in the analysis of each specific parameter. To assess change from baseline, a baseline measurement is also required.

Details on the approach to handling missing data for safety analyses are provided in Section 8.6 Statistical Methods.

8.6 Statistical Methods

8.6.1 Statistical Methods for Efficacy Analyses

This section describes the statistical methods that address the primary and secondary objectives.

For the primary efficacy endpoint of ORR, the point estimate, 95% confidence interval, and p-value for testing the response rate is greater than the historical control (10%) will be provided using exact binomial distribution. Subjects in the primary analysis population (FAS) without response data will be counted as non-responder.

For PFS, DOR and OS endpoints, Kaplan-Meier (KM) curves and median estimates from the KM curves will be provided as appropriate. Table 8 summarizes the efficacy analyses.

Table 8 Analysis Strategy for Efficacy Variables

Endpoint/Variable‡ (Description, Time Point)	Statistical Method	Analysis Population	Missing Data Approach
Primary Endpoint and Hypothesis			
ORR • RECIST 1.1, Central independent radiology review Hypotheses: ORR per RECIST 1.1 by the central independent radiology review is greater than historical control (10%).	Exact test of binomial parameter	FAS	Subjects with missing data are considered non-responders
Secondary Endpoints			
DOR • RECIST 1.1, Central independent radiology review • irRECIST, Central independent radiology review	Summary statistics using Kaplan-Meier method	All responders	Non-responders are excluded from analysis
PFS • RECIST 1.1, Central independent radiology review • irRECIST, Central independent radiology review	Summary statistics using Kaplan-Meier method	FAS	Censored at last assessment
ORR • irRECIST, Central independent radiology review	Exact test of binomial parameter	FAS	Subjects with missing data are considered non-responders
OS	Summary statistics using Kaplan-Meier method	FAS	Censored at last known alive date

8.6.2 Statistical Methods for Safety Analyses

Safety and tolerability will be assessed by clinical review of all relevant parameters including adverse experiences (AEs), laboratory tests and vital signs.

Summary statistics (counts, percentage, mean, standard deviation, etc.) will be provided for the safety endpoints as appropriate. The summary statistics of count and percentage will be provided for the incidence rate of any AE, any serious AE, any Grade 3-5 AE, any drug-related AE, any serious and drug-related AE, any Grade 3-5 and drug-related AE, dose

interrupted due to AE, discontinuation due to AE, any immune-related AE (irAE), death and specific AEs.

The summary statistics of mean and standard deviation will be provided for change from Baseline Results (Labs and Vital Signs) within each treatment cycle. The summary statistics of count and percentage will be provided for laboratory worsening from Baseline in terms of CTCAE grades.

8.6.3 Summaries of Baseline Characteristics, Demographics, and Other Analyses

The number and percentage of subjects screened, randomized, the primary reasons for screening failure, and the primary reason for discontinuation will be displayed. Demographic variables (e.g., age, gender), baseline characteristics, primary and secondary diagnoses, and prior and concomitant therapies will be summarized either by descriptive statistics or categorical tables.

8.6.4 Statistical Methods for Immunogenicity/pharmacokinetics endpoints Analyses

Summary statistics (mean, standard deviation and range) will be provided for pharmacokinetics measures of MK-3475 and appropriate plots will be generated on pharmacokinetic profiles.

8.7 Interim Analyses

No interim analyses are planned in this trial.

8.8 Multiplicity

The false positive rate for testing the primary efficacy hypothesis is controlled at 0.025 (1-sided). No additional multiplicity adjustment is proposed.

8.9 Sample Size and Power Calculations

In this study, approximately total 80 subjects with advanced melanoma will be enrolled.

With a sample size of 80, the study has 90% power to reject the null hypothesis of ORR=10% with a one-sided type I error rate of 2.5% if the true ORR is 24%. The null hypothesis rate of 10% is based on the historic response rate in large phase III trials for standard single agent chemotherapy in melanoma [20-31]. The actual number of subjects enrolled may be larger than 80 to ensure that at least 80 subjects are included in the primary endpoint analysis.

8.10 Subgroup Analyses and Effect of Baseline Factors

To determine whether the treatment effect is consistent across various subgroups, the estimate for the primary and secondary endpoints will be provided within each category of each subgroup. The following are examples of classification variables:

- PD-L1 (negative vs. positive)
- Subjects with advanced mucosal melanoma(yes vs. no)
- LDH (normal vs. high)
- BRAF status (negative vs. positive)

In addition, a Forest plot will be produced, which provides the estimated point estimates and confidence intervals for the treatment effect across the categories of subgroups listed above.

8.11 Compliance (Medication Adherence)

Drug accountability data for MK-3475 will be collected during the study. Any deviation from protocol-directed administration will be reported.

8.12 Extent of Exposure

Extent of Exposure for a subject is defined as number of cycles in which the subject receives the study medication infusion. Summary statistics will be provided on Extent of Exposure for ASaT population.

9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.1 Investigational Product

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

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

Table 9 Product Descriptions

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

9.2 Packaging and Labeling Information

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

Subjects will receive open label vials every 3 weeks (Q3W).

9.3 Clinical Supplies Disclosure

This trial is open-label; therefore, the subject, the trial site personnel, the Sponsor and/or designee are not blinded. Treatment (name, strength or potency) 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 Discard/Destruction/Returns and Reconciliation

The investigator is responsible for keeping accurate records of the clinical supplies received from the Sponsor or designee, the amount dispensed to and returned by the subjects and the amount remaining at the conclusion of the trial. For all trial sites, the local country Sponsor personnel or designee will provide appropriate documentation that must be completed for drug accountability and return, or local discard and destruction if appropriate. Where local discard and destruction is appropriate, the investigator is responsible for ensuring that a local discard/destruction procedure is documented.

9.6 Standard Policies

Trial site personnel will have access to a central electronic treatment allocation/randomization system (IVRS/IWRS system) to allocate subjects, to assign treatment to subjects and to manage the distribution of clinical supplies. Each person accessing the IVRS system must be assigned an individual unique PIN. They must use only their assigned PIN to access the system, and they must not share their assigned PIN with anyone.

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

10.1 Confidentiality

10.1.1 Confidentiality of Data

By signing this protocol, the investigator affirms to the Sponsor that information furnished to the investigator by the Sponsor will be maintained in confidence, and such information will be divulged to the institutional review board, ethics review committee (IRB/ERC) or similar or expert committee; affiliated institution and employees, only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees. Data generated by this trial will be considered confidential by the investigator, except to the extent that it is included in a publication as provided in the Publications section of this protocol.

10.1.2 Confidentiality of Subject Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), IRB/ERC, or regulatory authority representatives may consult and/or copy trial documents in order to verify worksheet/case report form data. By signing the consent form, the subject agrees to this process. If trial documents will be photocopied during the process of verifying worksheet/case report form information, the subject will be identified by unique code only; full names/initials will be masked prior to transmission to the Sponsor.

By signing this protocol, the investigator agrees to treat all subject data used and disclosed in connection with this trial in accordance with all applicable privacy laws, rules and regulations.

10.1.3 Confidentiality of Investigator Information

By signing this protocol, the investigator recognizes that certain personal identifying information with respect to the investigator, and all subinvestigators and trial site personnel, may be used and disclosed for trial management purposes, as part of a regulatory submissions, and as required by law. This information may include:

1. name, address, telephone number and e-mail address;
2. hospital or clinic address and telephone number;
3. curriculum vitae or other summary of qualifications and credentials; and
4. other professional documentation.

Consistent with the purposes described above, this information may be transmitted to the Sponsor, and subsidiaries, affiliates and agents of the Sponsor, in your country and other countries, including countries that do not have laws protecting such information. Additionally, the investigator's name and business contact information may be included when reporting certain serious adverse events to regulatory authorities or to other investigators. By signing this protocol, the investigator expressly consents to these uses and disclosures.

If this is a multicenter trial, in order to facilitate contact between investigators, the Sponsor may share an investigator's name and contact information with other participating investigators upon request.

10.1.4 Confidentiality of IRB/IEC Information

The Sponsor is required to record the name and address of each IRB/IEC member that reviews and approves this trial. The Sponsor is also required to document that each IRB/IEC meets regulatory and ICH GCP requirements by requesting and maintaining records of the names and qualifications of the IRB/IEC members and to make these records available for regulatory agency review upon request by those agencies.

10.2 Compliance with Financial Disclosure Requirements

Financial Disclosure requirements are outlined in the US Food and Drug Administration Regulations, Financial Disclosure by Clinical Investigators (21 CFR Part 54). It is the

Sponsor's responsibility to determine, based on these regulations, whether a request for Financial Disclosure information is required. It is the investigator's/subinvestigator's responsibility to comply with any such request.

The investigator/subinvestigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, commonly known as a financial disclosure form, provided by the Sponsor. The investigator/subinvestigator(s) also consent to the transmission of this information to the Sponsor in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

10.3 Compliance with Law, Audit and Debarment

By signing this protocol, the investigator agrees to conduct the trial in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of Good Clinical Practice (e.g., International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice: Consolidated Guideline and other generally accepted standards of good clinical practice); and all applicable federal, state and local laws, rules and regulations relating to the conduct of the clinical trial.

The Code of Conduct, a collection of goals and considerations that govern the ethical and scientific conduct of clinical investigations sponsored by Merck, is provided in Section 12.1 - Merck Code of Conduct for Clinical Trials.

The investigator also agrees to allow monitoring, audits, IRB/ERC review and regulatory authority inspection of trial-related documents and procedures and provide for direct access to all trial-related source data and documents.

The investigator agrees not to seek reimbursement from subjects, their insurance providers or from government programs for procedures included as part of the trial reimbursed to the investigator by the Sponsor.

The investigator shall prepare and maintain complete and accurate trial documentation in compliance with Good Clinical Practice standards and applicable federal, state and local laws, rules and regulations; and, for each subject participating in the trial, provide all data, and, upon completion or termination of the clinical trial, submit any other reports to the Sponsor as required by this protocol or as otherwise required pursuant to any agreement with the Sponsor.

Trial documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the trial site upon request for inspection, copying, review and audit at reasonable times by representatives of the Sponsor or any regulatory authorities. The investigator agrees to promptly take any reasonable steps that are requested by the Sponsor as a result of an audit to cure deficiencies in the trial documentation and worksheets/case report forms.

The investigator must maintain copies of all documentation and records relating to the conduct of the trial in compliance with all applicable legal and regulatory requirements. This

documentation includes, but is not limited to, the protocol, worksheets/case report forms, advertising for subject participation, adverse event reports, subject source data, correspondence with regulatory authorities and IRBs/ERCs, consent forms, investigator's curricula vitae, monitor visit logs, laboratory reference ranges, laboratory certification or quality control procedures and laboratory director curriculum vitae. By signing this protocol, the investigator agrees that documentation shall be retained until at least 2 years after the last approval of a marketing application in an ICH region or until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. Because the clinical development and marketing application process is variable, it is anticipated that the retention period can be up to 15 years or longer after protocol database lock. The Sponsor will determine the minimum retention period and notify the investigator when documents may be destroyed. The Sponsor will determine the minimum retention period and upon request, will provide guidance to the investigator when documents no longer need to be retained. The sponsor also recognizes that documents may need to be retained for a longer period if required by local regulatory requirements. All trial documents shall be made available if required by relevant regulatory authorities. The investigator must consult with and obtain written approval by the Sponsor prior to destroying trial and/or subject files.

ICH Good Clinical Practice guidelines recommend that the investigator inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.

The investigator will promptly inform the Sponsor of any regulatory authority inspection conducted for this trial.

Persons debarred from conducting or working on clinical trials by any court or regulatory authority will not be allowed to conduct or work on this Sponsor's trials. The investigator will immediately disclose in writing to the Sponsor if any person who is involved in conducting the trial is debarred or if any proceeding for debarment is pending or, to the best of the investigator's knowledge, threatened.

In the event the Sponsor prematurely terminates a particular trial site, the Sponsor will promptly notify that trial site's IRB/IEC.

According to European legislation, a Sponsor must designate an overall coordinating investigator for a multi-center trial (including multinational). When more than one trial site is open in an EU country, Merck, as the Sponsor, will designate, per country, a national principal coordinator (Protocol CI), responsible for coordinating the work of the principal investigators at the different trial sites in that Member State, according to national regulations. For a single-center trial, the Protocol CI is the principal investigator. In addition, the Sponsor must designate a principal or coordinating investigator to review the trial report that summarizes the trial results and confirm that, to the best of his/her knowledge, the report accurately describes the conduct and results of the trial [Clinical Study Report (CSR) CI]. The Sponsor may consider one or more factors in the selection of the individual to serve as the Protocol CI and or CSR CI (e.g., availability of the CI during the anticipated review process, thorough understanding of clinical trial methods, appropriate enrollment of subject cohort, timely achievement of trial milestones). The Protocol CI must be a participating trial investigator.

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. Merck, as Sponsor of this trial, will review this protocol and submit the information necessary to fulfill these requirements. Merck entries are not limited to FDAMA/FDAAA mandated trials. 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.

By signing this protocol, the investigator acknowledges that the statutory obligations under FDAMA/FDAAA are that of the Sponsor and agrees not to submit any information about this trial or its results to the Clinical Trials Data Bank.

10.5 Quality Management System

By signing this protocol, the Sponsor agrees to be responsible for implementing and maintaining a quality management system with written development procedures and functional area standard operating procedures (SOPs) to ensure that trials are conducted and data are generated, documented, and reported in compliance with the protocol, accepted standards of Good Clinical Practice, and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the clinical trial.

10.6 Data Management

The investigator or qualified designee is responsible for recording and verifying the accuracy of subject data. By signing this protocol, the investigator acknowledges that his/her electronic signature is the legally binding equivalent of a written signature. By entering his/her electronic signature, the investigator confirms that all recorded data have been verified as accurate.

Detailed information regarding Data Management procedures for this protocol will be provided separately.

10.7 Publications

This trial is intended for publication, even if terminated prematurely. Publication may include any or all of the following: posting of a synopsis online, abstract and/or presentation at a scientific conference, or publication of a full manuscript. The Sponsor will work with the authors to submit a manuscript describing trial results within 12 months after the last data become available, which may take up to several months after the last subject visit in some cases such as vaccine trials. However, manuscript submission timelines may be extended on OTC trials. For trials intended for pediatric-related regulatory filings, the investigator agrees to delay publication of the trial results until the Sponsor notifies the investigator that all relevant regulatory authority decisions on the trial drug have been made with regard to pediatric-related regulatory filings. Merck will post a synopsis of trial results for approved products on www.clinicaltrials.gov by 12 months after the last subject's last visit for the

primary outcome, 12 months after the decision to discontinue development, or product marketing (dispensed, administered, delivered or promoted), whichever is later.

These timelines may be extended for products that are not yet marketed, if additional time is needed for analysis, to protect intellectual property, or to comply with confidentiality agreements with other parties. Authors of the primary results manuscript will be provided the complete results from the Clinical Study Report, subject to the confidentiality agreement. When a manuscript is submitted to a biomedical journal, the Sponsor's policy is to also include the protocol and statistical analysis plan to facilitate the peer and editorial review of the manuscript. If the manuscript is subsequently accepted for publication, the Sponsor will allow the journal, if it so desires, to post on its website the key sections of the protocol that are relevant to evaluating the trial, specifically those sections describing the trial objectives and hypotheses, the subject inclusion and exclusion criteria, the trial design and procedures, the efficacy and safety measures, the statistical analysis plan, and any amendments relating to those sections. The Sponsor reserves the right to redact proprietary information.

For multicenter trials, subsequent to the multicenter publication (or after public disclosure of the results online at www.clinicaltrials.gov if a multicenter manuscript is not planned), an investigator and his/her colleagues may publish their data independently. In most cases, publication of individual trial site data does not add value to complete multicenter results, due to statistical concerns. In rare cases, publication of single trial site data prior to the main paper may be of value. Limitations of single trial site observations in a multicenter trial should always be described in such a manuscript.

Authorship credit should be based on 1) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; and 3) final approval of the version to be published. Authors must meet conditions 1, 2 and 3. Significant contributions to trial execution may also be taken into account to determine authorship, provided that contributions have also been made to all three of the preceding authorship criteria. Although publication planning may begin before conducting the trial, final decisions on authorship and the order of authors' names will be made based on participation and actual contributions to the trial and writing, as discussed above. The first author is responsible for defending the integrity of the data, method(s) of data analysis and the scientific content of the manuscript.

The Sponsor must have the opportunity to review all proposed abstracts, manuscripts or presentations regarding this trial 45 days prior to submission for publication/presentation. Any information identified by the Sponsor as confidential must be deleted prior to submission; this confidentiality does not include efficacy and safety results. Sponsor review can be expedited to meet publication timelines.

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12.0 APPENDICES

12.1 Merck Code of Conduct for Clinical Trials

Merck*
Code of Conduct for Clinical Trials

I. Introduction

A. Purpose

Merck, through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, implementing, conducting, analyzing and reporting these trials in compliance with the highest ethical and scientific standards. Protection of subject safety is the overriding concern in the design of clinical trials. In all cases, Merck clinical trials will be conducted in compliance with local and/or national regulations and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

Such standards shall be endorsed for all clinical interventional investigations sponsored by Merck irrespective of the party (parties) employed for their execution (e.g., contract research organizations, collaborative research efforts). This Code is not intended to apply to trials which are observational in nature, or which are retrospective. Further, this Code does not apply to investigator-initiated trials which are not under the control of Merck.

II. Scientific Issues

A. Trial Conduct

1. Trial Design

Except for pilot or estimation trials, clinical trial protocols will be hypothesis-driven to assess safety, efficacy and/or pharmacokinetic or pharmacodynamic indices of Merck or comparator products. Alternatively, Merck may conduct outcomes research trials, trials to assess or validate various endpoint measures, or trials to determine subject preferences, etc.

The design (i.e., subject population, duration, statistical power) must be adequate to address the specific purpose of the trial. Research subjects must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

Merck selects investigative sites based on medical expertise, access to appropriate subjects, adequacy of facilities and staff, previous performance in Merck trials, as well as budgetary considerations. Prior to trial initiation, sites are evaluated by Merck personnel to assess the ability to successfully conduct the trial.

3. Site Monitoring/Scientific Integrity

Trial sites are monitored to assess compliance with the trial protocol and general principles of Good Clinical Practice. Merck reviews clinical data for accuracy, completeness and consistency. Data are verified versus source documentation according to standard operating procedures. Per Merck policies and procedures, if fraud, misconduct or serious GCP-non-Compliance are suspected, the issues are promptly investigated. When necessary, the clinical site will be closed, the responsible regulatory authorities and ethics review committees notified and data disclosed accordingly.

B. Publication and Authorship

To the extent scientifically appropriate, Merck seeks to publish the results of trials it conducts. Some early phase or pilot trials are intended to be hypothesis-generating rather than hypothesis testing. In such cases, publication of results may not be appropriate since the trial may be underpowered and the analyses complicated by statistical issues of multiplicity.

Merck's policy on authorship is consistent with the requirements outlined in the ICH-Good Clinical Practice guidelines. In summary, authorship should reflect significant contribution to the design and conduct of the trial, performance or interpretation of the analysis, and/or writing of the manuscript. All named authors must be able to defend the trial results and conclusions. Merck funding of a trial will be acknowledged in publications.

III. Subject Protection

A. IRB/ERC review

All clinical trials will be reviewed and approved by an independent IRB/ERC before being initiated at each site. Significant changes or revisions to the protocol will be approved by the IRB/ERC prior to implementation, except that changes required urgently to protect subject safety and well-being may be enacted in anticipation of IRB/ERC approval. For each site, the IRB/ERC and Merck will approve the subject informed consent form.

B. Safety

The guiding principle in decision-making in clinical trials is that subject welfare is of primary importance. Potential subjects will be informed of the risks and benefits of, as well as alternatives to, trial participation. At a minimum, trial designs will take into account the local standard of care. Subjects are never denied access to appropriate medical care based on participation in a Merck clinical trial.

All participation in Merck clinical trials is voluntary. Subjects are enrolled only after providing informed consent for participation. Subjects may withdraw from a Merck trial at any time, without any influence on their access to, or receipt of, medical care that may otherwise be available to them.

C. Confidentiality

Merck is committed to safeguarding subject confidentiality, to the greatest extent possible. Unless required by law, only the investigator, sponsor (or representative) and/or regulatory authorities will have access to confidential medical records that might identify the research subject by name.

D. Genomic Research

Genomic Research will only be conducted in accordance with informed consent and/or as specifically authorized by an Ethics Committee.

IV. Financial Considerations

A. Payments to Investigators

Clinical trials are time- and labor-intensive. It is Merck's policy to compensate investigators (or the sponsoring institution) in a fair manner for the work performed in support of Merck trials. Merck does not pay incentives to enroll subjects in its trials. However, when enrollment is particularly challenging, additional payments may be made to compensate for the time spent in extra recruiting efforts.

Merck does not pay for subject referrals. However, Merck may compensate referring physicians for time spent on chart review to identify potentially eligible subjects.

B. Clinical Research Funding

Informed consent forms will disclose that the trial is sponsored by Merck, and that the investigator or sponsoring institution is being paid or provided a grant for performing the trial. However, the local IRB/ERC may wish to alter the wording of the disclosure statement to be consistent with financial practices at that institution. As noted above, publications resulting from Merck trials will indicate Merck as a source of funding.

C. Funding for Travel and Other Requests

Funding of travel by investigators and support staff (e.g., to scientific meetings, investigator meetings, etc.) will be consistent with local guidelines and practices including, in the U.S., those established by the American Medical Association (AMA).

V. Investigator Commitment

Investigators will be expected to review Merck's Code of Conduct as an appendix to the trial protocol, and in signing the protocol, agree to support these ethical and scientific standards.

* In this document, "Merck" refers to Merck Sharp & Dohme Corp. and Schering Corporation, each of which is a subsidiary of Merck & Co., Inc. Merck is known as MSD outside of the United States and Canada. As warranted by context, Merck also includes affiliates and subsidiaries of Merck & Co., Inc."

12.2 ECOG Performance Status

GRADE	ECOG PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

*Oken M, Creech R, Tormey D, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5:649-655

http://ecog-acrin.org/resources/ecog-performance-status

12.3 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).

12.4 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.

*REFERENCE:

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

12.5 Clinical Study Conduct System

Clinical study conduct system in China is provided in Attachment by Chinese language.

12.6 List of Abbreviations

Abbreviation/Term	Definition
AE	Adverse Event
ADA	Anti-Drug Antibodies
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
AP	Alkaline Phosphatase
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
ß-HCG	Beta Human Chorionic Gonadotropin
CI	Confidence Interval
CNS	Central Nervous System
CR	Complete Response
CrCl	Calculated Creatinine Clearance
CRF	Case Report Form
CSR	Clinical Study Report
CT	Computed Tomography
CTCAE	Common Toxicity Criteria for Adverse Events
CTLA-4	Cytotoxic T-Lymphocyte-Associated Antigen-4
DNA	Deoxyribonucleic acid
DOR	Duration of Response
ECI	Events of Clinical Interest
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organization for Research and Treatment of Cancer
ERC	Ethics Review Committee
FBR	Future Biomedical Research
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FDAMA	Food and Drug Administration Modernization Act
FNA	Fine Needle Aspirate
FT3	Free Triiodothyronine
FT4	Free Thyroxine
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
HBsAg	Hepatitis B surface Antigen
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IHC	Immunohistochemistry
INR	International Normalized Ratio
IPI	Ipilimumab

Abbreviation/Term	Definition
irAEs	Immune-related Adverse Events
irRECIST	Modification of RECIST 1.1
IRB	Institutional Review Board
IRC	Independent Central Review
IV	Intravenous
Kg	Kilogram
LDH	Lactate Dehydrogenase
mAb	Monoclonal Antibody
mcL	Microliters
Mg	Milligram
Mg/kg	Milligram per Kilogram
mL	milliliter
MRI	Magnetic Resonance Imaging
MSD	Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
NA or N/A	Not Applicable
NCI	National Cancer Institute
NSCLC	Non-Small Cell Lung Cancer
ORR	Overall Response Rate
OS	Overall Survival
OTC	Over-the-counter
PD	Progressive Disease
PD-1	Programmed Cell Death-1
PFS	Progression Free Survival
PGt	Pharmacogenetic
PK	Pharmacokinetic
PK/PD	Pharmacokinetic/Pharmacodynamic
PR	Partial Response
PT	Prothrombin Time
RCC	Renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic Acid
Q3W	Every 3 Weeks
SAE	Serious Adverse Events
SAP	Statistical Analysis Plan
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SIM	Site Imaging Manual
SOP	Standard Operating Procedures
T1DM	Type 1 Diabetes Mellitus
TCM	Traditional Chinese Medicine
TSH	Thyroid Stimulating Hormone
ULN	Upper Limit of Normal
US	United States
WBC	White Blood Cell

13.0 SIGNATURES

13.1 Sponsor's Representative

TYPED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	

13.2 Investigator

I agree to conduct this clinical trial in accordance with the design outlined in this protocol and to abide by all provisions of this protocol (including other manuals and documents referenced from this protocol). I agree to conduct the trial in accordance with generally accepted standards of Good Clinical Practice. I also agree to report all information or data in accordance with the protocol and, in particular, I agree to report any serious adverse events as defined in Section 7.0 – Assessing and Recording Adverse Events. I also agree to handle all clinical supplies provided by the Sponsor and collect and handle all clinical specimens in accordance with the protocol. I understand that information that identifies me will be used and disclosed as described in the protocol, and that such information may be transferred to countries that do not have laws protecting such information. Since the information in this protocol and the referenced Investigator's Brochure is confidential, I understand that its disclosure to any third parties, other than those involved in approval, supervision, or conduct of the trial is prohibited. I will ensure that the necessary precautions are taken to protect such information from loss, inadvertent disclosure or access by third parties.

TYPED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	