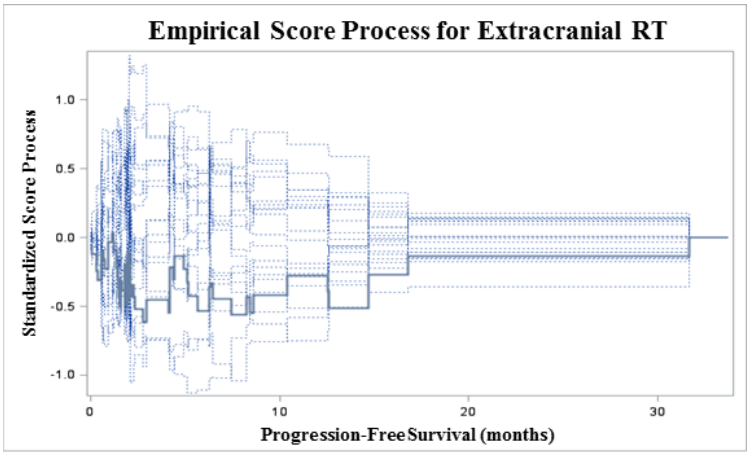
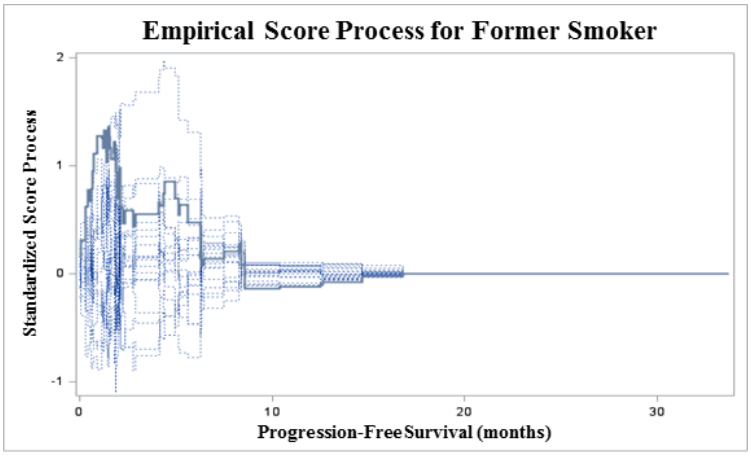
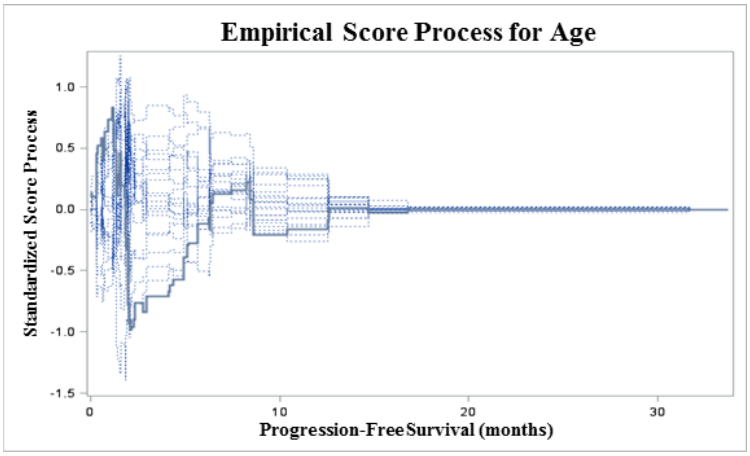
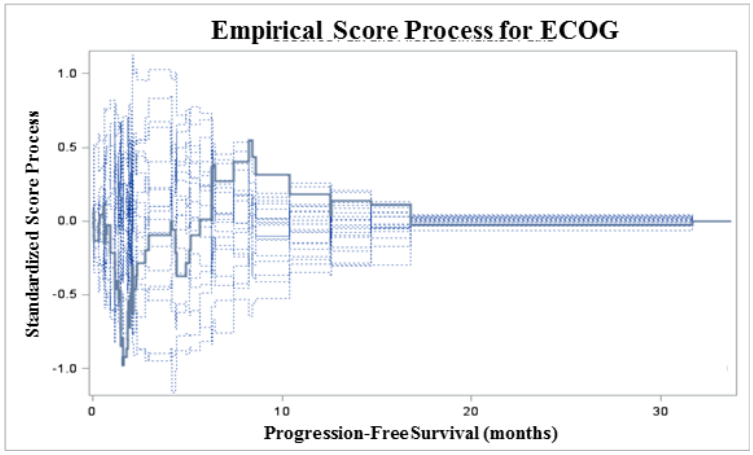
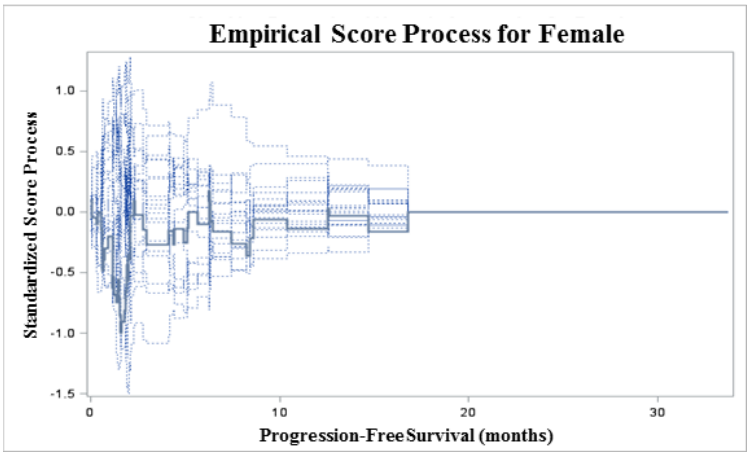
Proportional Hazard Assumption Verification: Multivariate Progression-Free Survival Model Evaluating Prior Extracranial Radiation Therapy

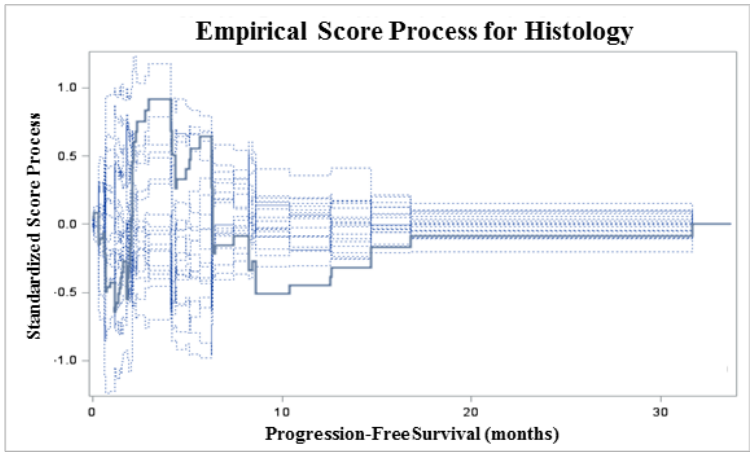




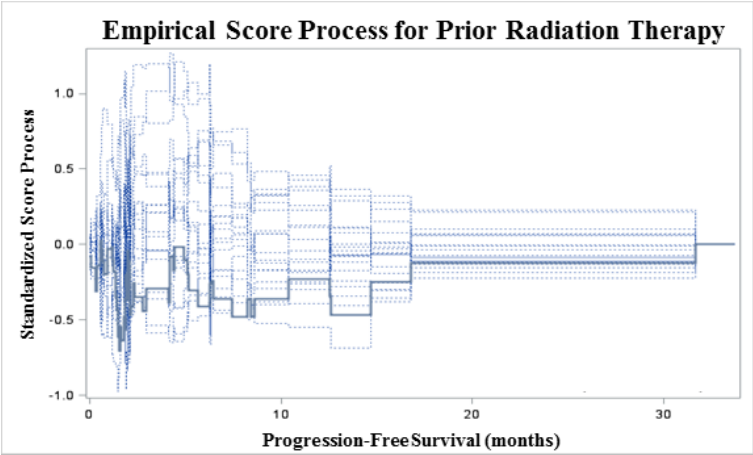


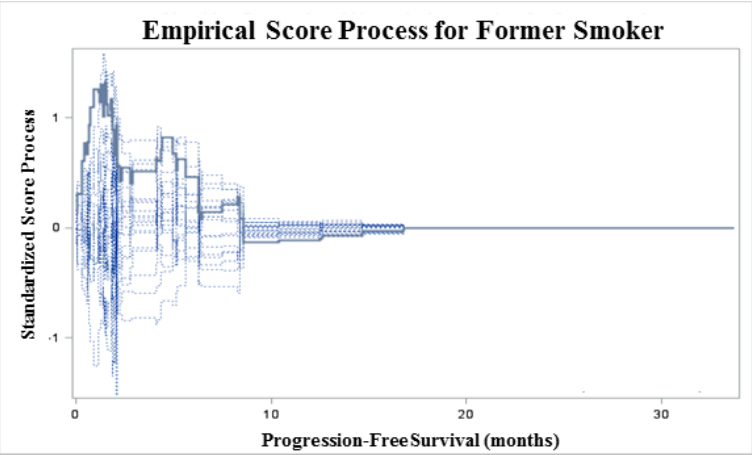


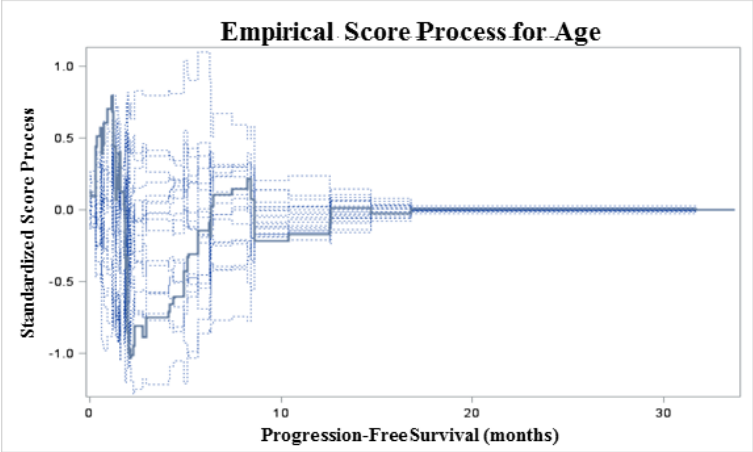


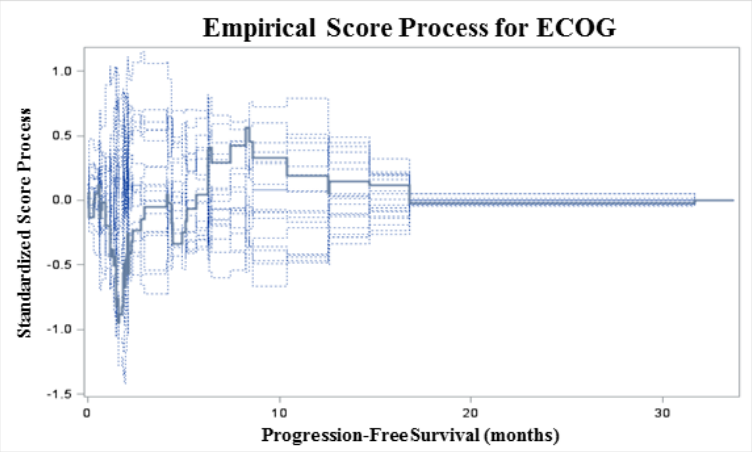


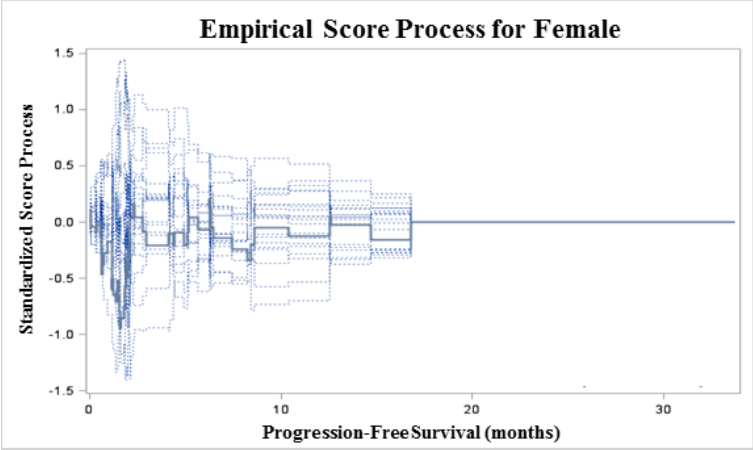
Proportional Hazard Assumption Verification: Multivariate Progression-Free Survival Model Evaluating Prior Radiation Therapy

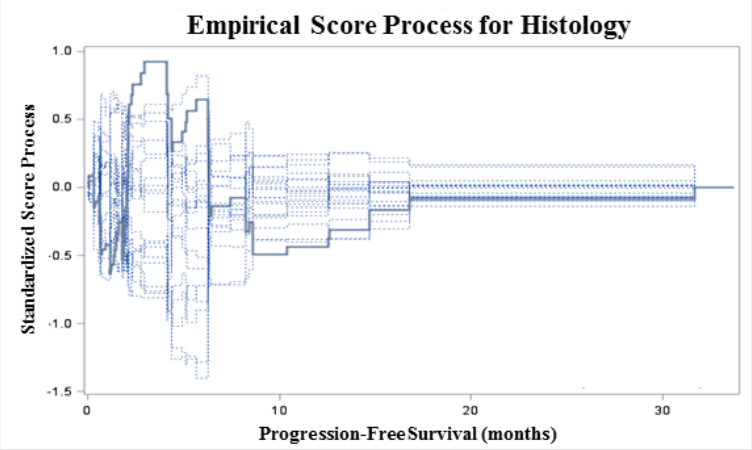




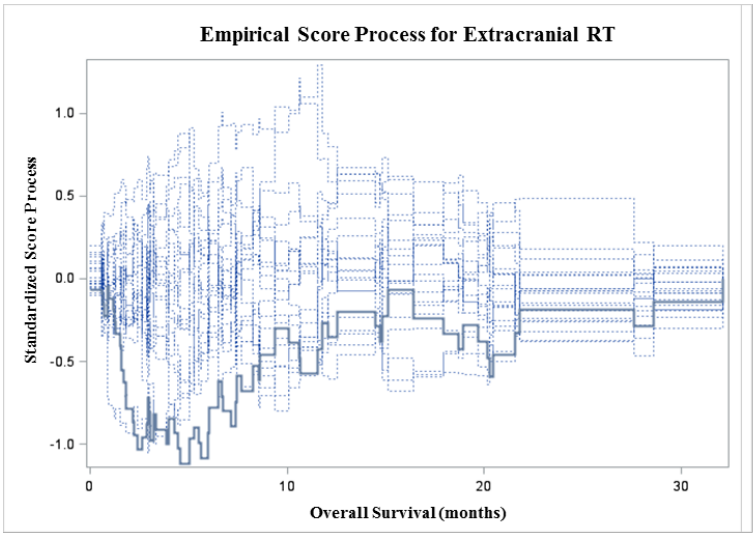


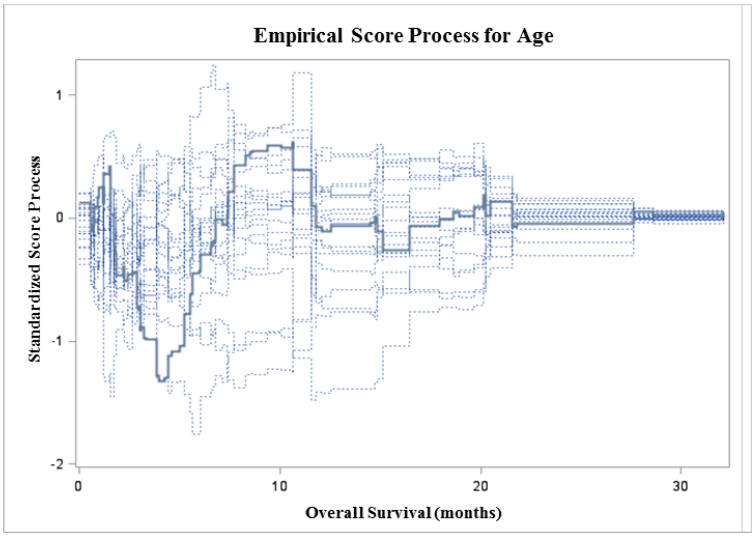


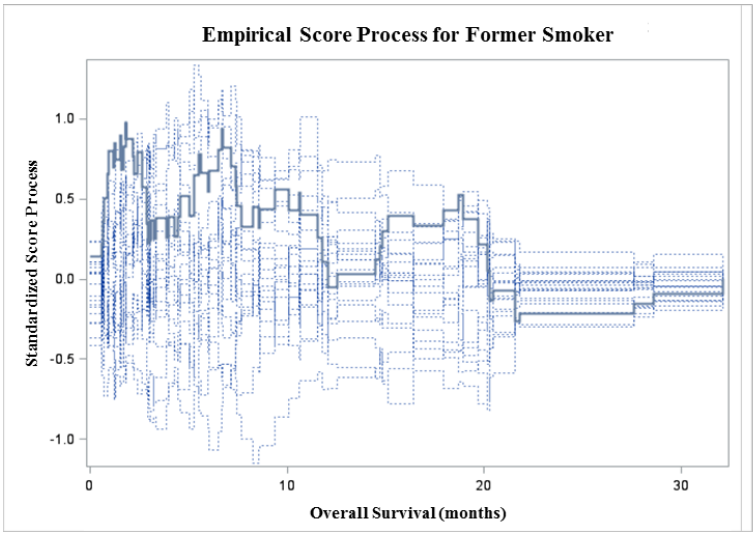


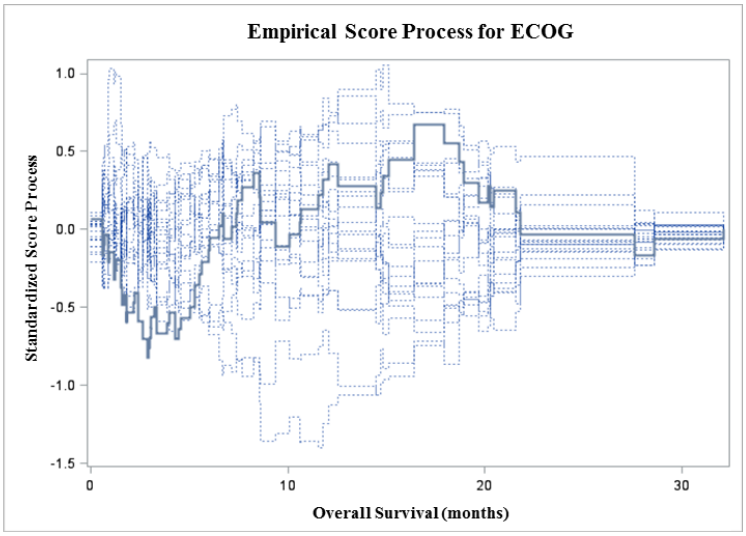


Proportional Hazard Assumption Verification: Multivariate Overall Survival Model Evaluating Prior Extracranial Radiation Therapy

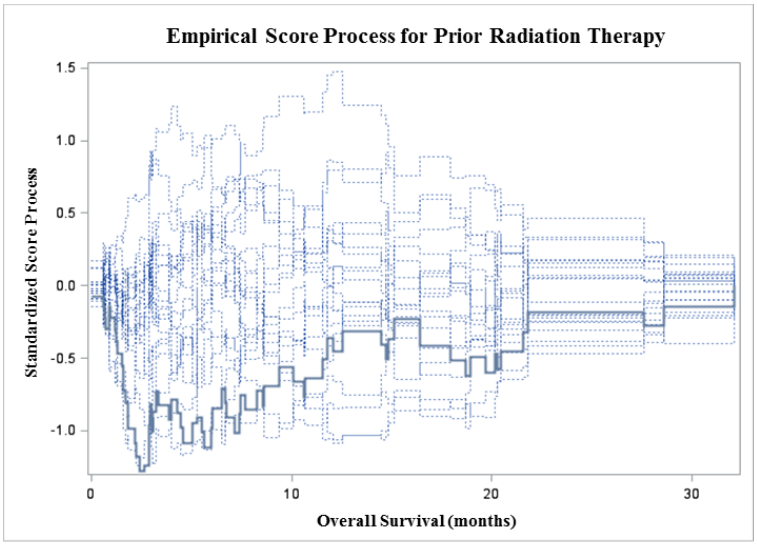


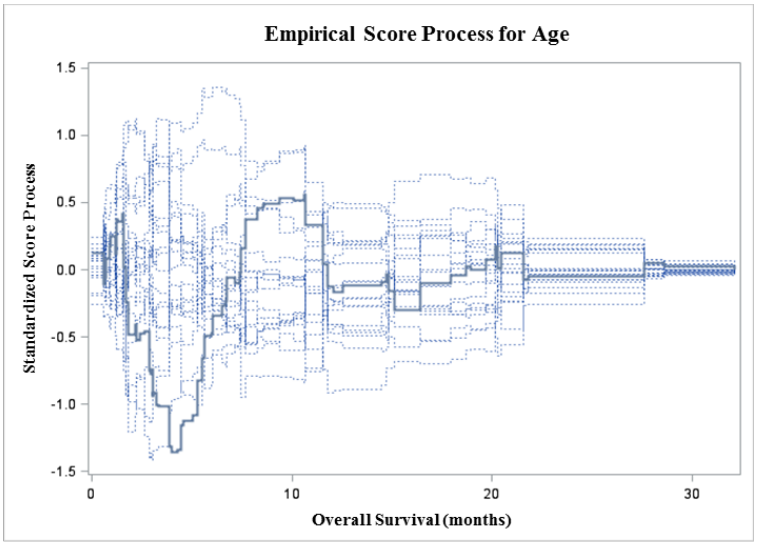


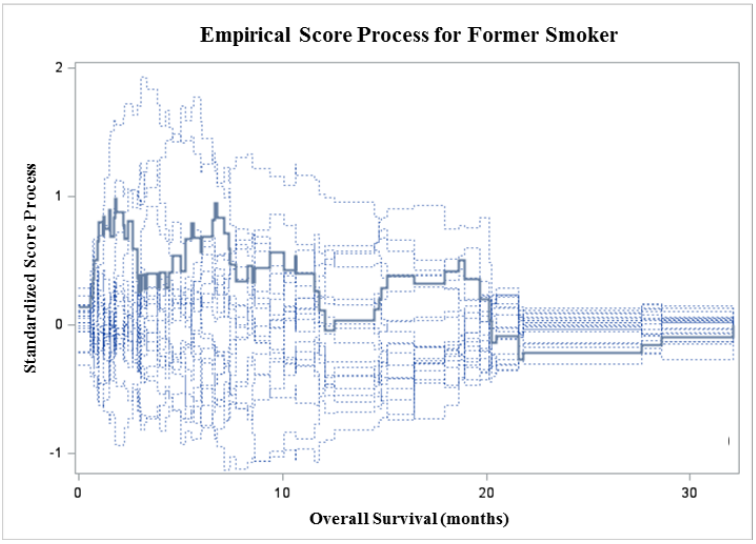


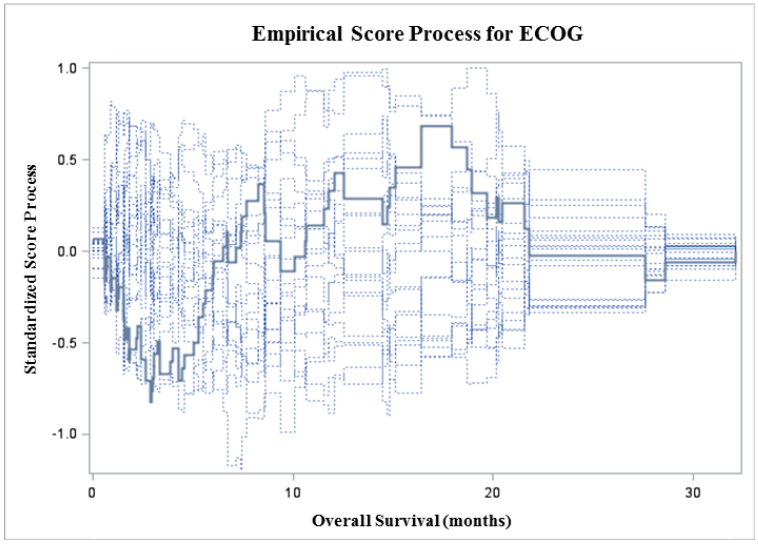


Proportional Hazard Assumption Verification: Multivariate Overall Survival Model Evaluating Prior Radiation Therapy









Predictors of a three-month minimum progression-free survival on univariate analysis

Factor	Odds Ratio	95% CI	*p*-value
Age	1·07	1·03-1·12	0·0015
Female vs Male	0·62	0·28-1·39	0·25
ECOG 1 vs ECOG 0	0·44	0·19-1·02	0·055
Former smokers vs Nonsmoker	3·36	1·44-7·83	0·0051
Adenocarcinoma & Other vs Squamous	0·21	0·07-0·65	0·0065
PD-L1 Positivity	0·71	0·20-2·53	0·59
PD-L1 % Expression	1·00	0·99-1·02	0·81
Number of Previous Systemic Therapies	0·81	0·63-1·06	0·12
Time Since Diagnosis	0·99	0·97-1·01	0·40
Stage IV vs Stage I-III at initial diagnosis*	0·48	0·20-1·18	0·11
Prior Extracranial Radiation Therapy	2·99	1·29-6·96	0·011
Prior Radiation Therapy	2·12	0·93-4·81	0·072

***All patients at trial entry had metastatic disease.**

Multivariate model evaluating any prior radiation therapy and a three-month minimum progression-free survival

Factor	Odds Ratio	95% CI	*p*-value
Age	1·08	1·02-1·14	0·0047
ECOG 1 vs ECOG 0	0·40	0·15-1·06	0·065
Adenocarcinoma & Other vs Squamous	0·29	0·08-1·02	0·054
Former smokers vs Nonsmoker	1·77	0·65-4·82	0·26
Prior Radiation Therapy	2·86	1·06-7·72	0·039

Multivariate model evaluating prior extracranial radiation therapy and a three-month minimum progression-free survival

Factor	Odds Ratio	95% CI	*p*-value
Age	1·08	1·03-1·14	0·0042
ECOG 1 vs ECOG 0	0·42	0·16-1·12	0·083
Adenocarcinoma & Other vs Squamous	0·31	0·08-1·10	0·069
Former smokers vs Nonsmoker	1·73	0·63-4·76	0·29
Prior Extracranial Radiation Therapy	3·72	1·33-10·36	0·012

Recorded Pulmonary Toxicity by CTCAE v4 Grading

Pulmonary Toxicity	Grades 1 - 2	Grade 3	Grade 4	Grade 5
Dyspnea	15	6	-	-
Cough	23		-	-
Wheezing	4	-	-	-
Pneumonitis	1	-	2	-
Respiratory Failure[1]	2	-	1	4

[1]Two cases of respiratory failure of < grade 4 were prospectively reported by the trial investigators. These adverse events (AEs) were incorrectly categorized according to CTCAE v4 criteria, since respiratory failure can only be categorized as ≥ grade 4. Instead these AEs should have been categorized as dyspnea, but are shown as originally recorded.

Treatment-Related Pulmonary Toxicity by CTCAE v4 Grading

Pulmonary Toxicity	Grades 1 - 2	Grade 3	Grade 4	Grade 5
Dyspnea	2	-	-	-
Pneumonitis	1	-	2	-

Protocol

This supplement contains the following items:

1. Original protocol, final protocol, summary of changes.
2. Original statistical analysis plan (included within protocol), final statistical analysis plan (included within protocol), summary of changes.

Merck's policy on posting of redacted study protocols on journal websites is described in Merck Guidelines for Publication of Clinical Trials in the Scientific Literature on the www.merck.com website.

For publicly posted protocols, Merck redacts the background and rationale sections because these sections may contain proprietary information. Merck also redacts the names of any individuals due to privacy issues. The appendices generally are not provided because they may be lengthy and contain non-essential information. The publicly posted protocol includes all the key sections that are relevant to evaluating the study, specifically those sections describing the study objectives and hypotheses, the patient inclusion and exclusion criteria, the study design and procedures, the efficacy and safety measures, the statistical analysis plan, and amendments relating to those sections.

This report may include approved and non-approved uses, formulations, or treatment regimens. The results reported may not reflect the overall profile of a product. Before prescribing any product mentioned this report, healthcare professionals should consult local prescribing information for the product approved in their country.

THIS PROTOCOL AMENDMENT AND ALL OF THE INFORMATION RELATING TO IT ARE CONFIDENTIAL AND PROPRIETARY PROPERTY OF MERCK SHARP & DOHME CORP., A SUBSIDIARY OF MERCK & CO., INC., WHITEHOUSE STATION, NJ, U.S.A.

SPONSOR:

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. (hereafter referred to as the **SPONSOR** or Merck)
One Merck Drive
P.O. Box 100
Whitehouse Station, NJ 08889-0100, U.S.A.

Protocol-specific Sponsor Contact information can be found in the Administrative Binder.

TITLE:

Phase I Study of Single Agent MK-3475 in Patients with Progressive Locally Advanced or Metastatic Carcinoma, Melanoma, and Non-Small Cell Lung Carcinoma

INVESTIGATOR:

PRIMARY:

CLINICAL PHASE: I

US IND NUMBER: 110,080

SITE:

INSTITUTIONAL REVIEW BOARD/ETHICS REVIEW COMMITTEE:

Table of Contents

SUMMARY OF CHANGES

PRIMARY REASON(S) FOR THIS AMENDMENT

The primary reasons for this amendment include changing the primary measure for assessment of tumor response to RECIST 1.1 by blinded central review, and immune-related response criteria (irRC) is now the secondary measure of tumor assessment. In addition, additional biomarker negative patients have been added to Part F-2.

Implementation of these objectives necessitates the following changes to the protocol:

- Addition of 20 patients with NSCLC to Part F-2 who are biomarker negative.
- Changing the statistical analysis plan

ADDITIONAL CHANGE(S) FOR THIS AMENDMENT

Throughout the protocol, procedures have been separately listed for Part A, Part B, Part C, Part D and Part F. Numerous minor modifications and corrections have been made throughout the document, those changes are summarized below.

In addition, typographical errors and inconsistencies were corrected throughout the document and are not listed here.

Section Number(s)	Section Title(s)	Description of Change(s)
1.4	Summary of Rationale	Eliminated incorrect reference to 2 mg/kg dosing in Part F-2 and replaced with 10 mg/kg every 2 weeks.
1.5	Sample	Correction - stratification “may” occur in Part F-2 patients by either weak or strong PD-L1 expression
1.6	Dosage/Dosage Form, Route, and Dose Regimen	Permit patients with NSCLC assigned to 2 mg/kg Q3W under amendment 06 to continue to be treated at that dose and escalation of dose to 10 mg/kg Q3W upon confirmation of PD.
1.7	Flow Chart	Part B: 2 Week Schedule – HLA collection moved from Screening to Cycle 1, as only allocated and randomized patients will have HLA samples collected.

1.7	Flow Chart	Parts B and D: Footnote 18 – Added clarifying language regarding timing of the scans and sentence added to clarify that a new baseline scan is required if the biopsy is obtained from a target lesion.
1.7	Flow Chart	Part B: Footnote 19 – Sentence added to clarify that ipi-refractory patients must have pre-trial scans sent to the central imaging vendor. Subsequent footnote numbers updated as appropriate.
1.7	Flow Chart	Part B: Footnote 20 – Provided additional guidance on collecting the newly obtained biopsy.
1.7	Flow Chart	Part D: Footnote 19 – Provided additional guidance on collecting the newly obtained biopsy.
1.7	Flow Chart	Part B: Footnote 21 - Updated to clarify which amendments archive tumor tissue is required for.
1.7	Flow Chart	Part B: Footnote 24- Updated to clarify which amendments HLA samples are required for.
1.7	Flow Chart	Part C – Footnote 18 - Added clarifying language regarding timing of the scans and sentence added to clarify that a new baseline scan is required if the biopsy is obtained from a target lesion.
1.7	Flow Chart	Part F: 2 and 3 Week Schedules – Footnote 18 - Added clarifying language regarding timing of the scans and sentence added to clarify that a new baseline scan is required if the biopsy is obtained from a target lesion.
1.7	Flow Chart	Part F: 2 and 3 Week Schedules – Footnote 20 – Removed 60 day time limit for duration of new biopsy to initiation of MK-3475, yet maintained that no intervening systemic therapy may have been received between the biopsy and MK-3475.
1.7	Flow Chart	Part F: 2 and 3 Week Schedules - Added a newly obtained biopsy or archival biopsy for ALK/EGFR testing is required if the sample is analyzed via the central vendor. This sample is in addition to the sample that is required for PD-L1 testing.
1.7	Flow Chart	Part F: 3 Week Schedule – Footnote 25 – added the following text: “pulse oximetry, forced expiratory flow 25-75% (FEF 25-75), and Peak Expiratory Flow (PEF)”
1.7	Flow Chart	Part F: 2 Week Schedule – Footnote 25 – added the following text: “pulse oximetry, forced expiratory flow 25-75% (FEF 25-75), Peak Expiratory Flow (PEF)”

1.7	Flow Chart	Part B, C, D, F: Follow Up – Footnote 11 – Changed so that survival follow up continues until no longer possible, and not only for up to 24 months after last dose.
1.7	Flow Chart	Follow-Up (Parts B, C, D, F) – Added Survival Follow-Up will continue until the Investigator is notified by the Sponsor to discontinue follow-up.
1.7	Flow Chart	Second Course Phase 2 Week Schedule – Added tumor imaging assessments at Week 9 and 18 for non-small cell lung cancer (NSCLC) patients, and modified corresponding Footnote 8 to reflect the NSCLC continuing imaging assessments.
1.7	Flow Chart	Second Course Phase: Follow Up – the following procedures were removed from the flow chart: 12-lead ECG, Pharmacokinetics, Immunoglobulins, PT/INR and aPTT, Auto-Antibodies, Anti-MK-3475 Antibodies. The corresponding footnotes were also removed: Footnotes 4, 6, 7, 8, 14. Footnote 11: changed so that survival follow up continues until no longer possible, and not only for up to 24 months after last dose.
2.1	Primary and Secondary Objectives	Clarified that all response assessments by RECIST 1.1 are primary and by irRC are secondary.
2.2	Patient Inclusion Criteria	Criterion 1, Part B – Ipilimumab-refractory patients: 4th bullet – correction < 10 mg/day prednisone changed to ≤ 10 mg/day.

2.2	Patient Inclusion Criteria	Criterion 1, Part F: 1st sub-bullet of 2nd bullet- clarified that patients in F-1 must be EGFR wild type and without ALK translocation. 2nd sub-bullet of 2nd bullet– removed the sequence requirement that patients must have progressed first on a tyrosine kinase inhibitor and then a platinum containing doublet. Clarified that the EGFR mutation must be sensitizing to EGFR tyrosine kinase inhibitors and added afatinib as an appropriate Tyrosine Kinase Inhibitor 4th bullet – added patients in F-1 must be naïve to systemic treatment for NSCLC and have Stage IV disease. Added an additional requirement that those patients with NSCLC who have a tumor in an anatomic location suggesting an impending catastrophic event should have that lesion radiated prior to study therapy.
2.3	Patient Exclusion Criteria	Criterion 1: Added that patients taking crizotinib must have a washout period of 10 days prior to dosing.
2.3	Patient Exclusion Criteria	Criterion 4: Permit patients taking physiologic replacement doses of corticosteroid to enter the study. The accepted maximal daily dose is defined.
2.3	Patient Exclusion Criteria	Criterion 6: Added patients must not have a known history of malignant primary brain tumor, malignant sarcoma, or another malignant primary solid tumor.
2.3	Patient Exclusion Criteria	Criterion 7: Removed confusing last sentence that warned investigators to consider that some patients may have asymptomatic brain metastases.
2.3	Patient Exclusion Criteria	Criterion 13: Added that patients with negative Hepatitis C antibody testing do not need HCV RNA testing.
2.4.1	Summary of Study Design	Patients whose imaging shows disease progression, if they are clinically stable, should have a confirmatory scan performed 4-6 weeks after the initial finding of progression. Additional minimal criteria have been added to allow a patient to continue in the study following disease progression to receive a confirmatory scan.

2.7.1	Efficacy Analysis	The primary measure for assessment of tumor response has been changed to RECIST 1.1 by blinded central review, and irRC is now the secondary measure of tumor assessment. Kaplan-Meier statistical methods will now be employed for time-to-response and overall response rate. In addition, overall response rate will be based on patients with at least 28 weeks of follow-up.
3.2.5.4.2.1	Pulmonary Function	This section is entirely new, and includes pulmonary assessments for patients in Part F.
3.2.5.4.5	Electrocardiogram	Corrections made to ensure this section and the Flow Charts match.
3.2.5.4.9	Guidelines for Dose Modification	Patients who experience the same SAE of the same NCI toxicity grade or greater with rechallenge of MK-3475 must discontinue from MK-35475. Patients who experience a Grade 3 Infusion Reaction should discontinue MK-3475.
3.2.5.4.10	Supportive Care Guidelines	Removed the bullet related to Events of Clinical Interest with a potential immunologic etiology (ECI-ie) which was repetitive of the information provided in 3.2.5.4.10.2.
3.2.5.4. 10.1	Pneumonitis	Permanent discontinuation of MK-3475 following ≥ Grade 3 adverse event.
3.2.5.4. 10.2	Adverse Events of Clinical Interest: Immune Related Adverse Events	Corrected title of reference ECI and irAE guidance document. Sentence added that oral or intravenous treatment with a corticosteroid should be considered depending on the type and severity of the irAE.
3.3.1.2	Efficacy Endpoints	Changed primary response rate endpoint to be based on RECIST 1.1 as determined by independent central review for Parts B, C, D, and F.
3.4.2	Recording Adverse Events	Sentence added that explains progression of cancer under study is not an adverse event unless considered drug related.
3.4.4	Reporting of Pregnancy	Changed number of days from 30 to 120 following the last dose of study medication that a patient or male patient's partner should report a pregnancy to the Sponsor.
3.4.5.1	Serious Adverse Experiences	Deleted the first sentence in the section. Added text indicating serious adverse events must be reported for at least 30 days following cessation of study medication, regardless of whether new anti-cancer therapy has been started or not.

3.4.9	Protocol-Specific Exceptions to Serious Experience Reporting	Updated text added to improve clarity.
3.5.2	Hypotheses/ Estimation	The primary endpoint has been changed to anti-tumor response rate based on RECIST 1.1 by blinded central reviewers. In addition response rate and disease control rate as assessed per irRC by the investigators in the ipilimumab-naïve population treated at 10 mg/kg in Part B enrolled through Amendment 04 will be analyzed for internal decision making.
3.5.3.1	Efficacy Endpoints	Response rate and disease control rate will serve at the primary efficacy endpoints only for the ipilimumab-naïve population treated at 10 mg/kg in Part B enrolled through Amendment 04, and only for internal decision purposes.
3.5.5.1	Efficacy Analysis	The primary measure for assessment of tumor response has been changed to RECIST 1.1 by blinded central review. Kaplan-Meier statistical methods will now be employed for time-to-response and overall response rate. In addition, overall response rate will be based on patients with at least 28 weeks of follow-up.
3.5.5.4	Predictive Biomarker Analyses	Added a paragraph to the end of the Validation section discussing handling of indeterminate PD-L1 expression results.
3.5.9	Interim Analyses	Clarified the interim analyses of the ipilimumab-naïve patients treated at 10 mg/kg and enrolled through Amendment 04 to be for internal decision making.

1. SUMMARY

1.1 TITLE

Phase I Study of Single Agent MK-3475 in Patients with Progressive Locally Advanced or Metastatic Carcinoma, Melanoma, and Non-Small Cell Lung Carcinoma.

1.2 INDICATION

For Part A, patients with a histologically or cytologically confirmed diagnosis of any type of carcinoma or of melanoma (MEL) who have progressive locally advanced or metastatic disease.

For Part B, patients with a histologically or cytologically confirmed diagnosis of MEL with progressive locally advanced or metastatic disease that is not amenable to definitive local therapy with curative intent.

For Part C, patients with a histologically or cytologically confirmed diagnosis of non-small cell lung cancer (NSCLC) with progressive locally advanced or metastatic disease after 2 prior systemic therapy regimens.

For Part D, patients with a histologically or cytologically confirmed diagnosis of MEL with progressive locally advanced or metastatic disease that is not amenable to definitive local therapy with curative intent.

For Part F, patients whose tumors express PD-L1 with a histologically or cytologically confirmed diagnosis of non-small cell lung cancer (NSCLC) with progressive locally advanced or metastatic disease after one or more prior systemic treatment regimens or naïve to systemic treatment.

1.3 SUMMARY OF RATIONALE

Redacted

Redacted

1.4 SUMMARY OF STUDY DESIGN

This is an open-label, Phase I study of intravenous (IV) MK-3475 in patients with progressive locally advanced or metastatic carcinomas, especially MEL or NSCLC. **Part A** of the study will use a traditional 3+3 design for dose escalation. Cohorts of 3-6 patients will be enrolled sequentially at escalating doses of 1, 3 and 10 mg/kg. Dose

escalation will continue until identification of MTD, up to a maximum dose of 10 mg/kg. Once the dose escalation is completed, additional patients will be enrolled to more fully characterize the PK profile. In **Part B**, patients with MEL will be enrolled at the preliminary RP2D(s) to characterize the tolerability and safety profile of the dose, and for preliminary evaluation of anti-tumor activity in MEL. Additionally, different doses and dosing schedules will be compared in a randomized fashion in patients with advanced melanoma. In **Part C**, patients with NSCLC will be enrolled at the preliminary RP2D(s) to characterize the tolerability and safety profile of the dose, and for preliminary evaluation of anti-tumor activity in NSCLC. In **Part D**, patients with MEL will be enrolled at 2 mg/kg and 10 mg/kg to evaluate the tolerability and safety profile of each dose, and for preliminary evaluation of anti-tumor activity in MEL. In **Part F-1**, patients without prior systemic therapy whose tumors express PD-L1 with NSCLC will be enrolled at 10 mg/kg Q2W and 10 mg/kg Q3W to characterize the tolerability and safety profile of MK-3475 monotherapy, and for evaluation of the dose and anti-tumor activity in NSCLC. In **Part F-2**, patients with prior systemic therapy whose tumors express PD-L1 with NSCLC will be enrolled at 10mg/kg Q3W and 10 mg/kg Q2W to characterize the tolerability and safety profile of MK-3475 monotherapy, and for evaluation of the dose and anti-tumor activity in NSCLC. A small cohort of previously-treated patients with at least two lines of systemic therapy whose tumors do not express PD-L1 will be enrolled and treated at a dose of 10 mg/kg Q2W. Part F will also evaluate the extent of tumor response that correlates with the degree of biomarker positivity in patients treated with MK-3475.

1.5 SAMPLE

A total of approximately 1067 eligible patients will be enrolled in this study, with approximately 28 patients in Part A, approximately 506 patients in Part B, approximately 35 patients in Part C, approximately 88 patients in Part D, and approximately 410 patients in Part F.

In Part A, patients with any type of carcinoma may be enrolled, and patients may have non-measurable disease. Patients in Part A will be distributed as follows:

- Dose escalation = 10 patients
- Part A-1 (PK expansion at MTD) (up to 10 mg/kg Q2W): 6 patients
- Part A-2 (PK expansion, intra-patient dose escalation, Q3W): 12 patients

In Part B, only patients with MEL may be enrolled (metastatic MEL or patients with locally advanced disease and not candidates for surgical resection or a definitive local therapy), and patients must have measurable disease (see Section 2.2 and Appendix 6.5). Part B will enroll approximately 506 patients distributed as described in Table 1-1.

Table 1-1

Patient Distribution in Part B

	10 mg/kg	2 mg/kg
Ipilimumab Naïve	61[1,3]	15[2,3]
Ipilimumab Treated	40[1,3]	0[3]
Ipilimumab Refractory	80[2,3]	80[2,3]
Ipilimumab Naïve or Treated	230[1,4]	

1 Includes patients with dosing schedules of Q2W and Q3W.
2 Dosing schedule is Q3W
3 Up through Amendment 001-06
4 Amendment 001- 07

Enrollment of patients at 2 mg/kg who are naïve to ipilimumab in Part B will begin once all 10 mg/kg patients in Part B are enrolled up through Amendment 04. All patients enrolled after the approval of Amendment 03 or approval of the administrative memo dated 06-Jan-2012, will be dosed Q3W with the exception of patients enrolled under Amendment 07.

Enrollment of the first 13 patients in Part B will be restricted to ipilimumab-naïve patients (which will serve as basis for the first interim analysis). The remaining patients will be enrolled without a hold to complete a total of 60 patients (40 ipilimumab-naïve and 20 ipilimumab-treated). With Amendment 04, an additional 55 patients (35 ipilimumab-naïve and 20 ipilimumab-treated) will be enrolled. With amendment 05, 60 ipilimumab-refractory patients will be enrolled. The ipilimumab-naïve, ipilimumab-treated and ipi-refractory cohorts are defined per eligibility criteria in Sections 2.2 and 2.3. With Amendment 06, the ipilimumab-refractory cohort will enroll an additional 100 patients for a total of 160 patients. The ipilimumab-refractory cohort will randomize up to 80 patients at 2 mg/kg and 80 patients at 10 mg/kg administered every 3 weeks (Q3W) who meet the ipilimumab-refractory eligibility criteria as provided in the current amendment in a 1:1 fashion, manually by the Sponsor, based on a computer-generated allocation schedule. Upon approval of Amendment 07, Part B will enroll an additional 230 patients irrespective of prior ipilimumab status. This cohort will randomize approximately 115 patients at 10 mg/kg Q2W and 115 patients at 10 mg/kg Q3W who meet the Part B eligibility criteria as provided in the current amendment in a 1:1 fashion, manually by the Sponsor, based on a computer-generated allocation schedule. If a patient is ipilimumab-refractory and BRAF V600E mutant, then one of the prior systemic treatment regimens must have included a vemurafenib, dabrafenib, or other approved BRAF or MEK inhibitors if allocated under Amendment 07. Ipilimumab naïve patients are allowed up to 2 prior systemic treatment regimens, one of which may have included prior treatment with a BRAF inhibitor.

In Part C, 35 patients with NSCLC may be enrolled (progressive metastatic or locally advanced NSCLC after treatment with two prior systemic regimens), and patients must

have measurable disease (see Section 2.2 and Appendix 6.5). All patients will be dosed Q3W.

In Part D, patients with MEL may be enrolled (metastatic MEL or patients with locally advanced disease and not candidates for surgical resection or a definitive local therapy), and patients must have measurable disease (see Section 2.2 and Appendix 6.5). Part D will enroll approximately 88 patients, randomized 1:1 manually by the Sponsor based on a computer-generated allocation schedule, to either 2 mg/kg or 10 mg/kg. All patients will be dosed Q3W.

Enrollment in Part D will be restricted to ipilimumab-naïve patients who are allowed up to 2 prior systemic treatment regimens.

In Part F, approximately 410 patients with metastatic or locally advanced NSCLC may be enrolled, and patients must have measureable disease (see Section 2.2 and Appendix 6.5).

In F-1 (treatment-naïve systemically), all patients' tumor tissue will be tested for expression of PD-L1, as determined by IHC, using a laboratory developed assay performed during Screening. Eighty-eight patients whose tumors express PD-L1, and are naïve to systemic treatment, will be randomized 1:1, manually by the Sponsor based on a computer-generated allocation schedule, to 10 mg/kg of MK-3475 at either Q2W or Q3W. An analytically validated assay PD-1L IHC assay will be used to determine the PD-L1 status of FFPE tumor samples.

In F-2 (previously-treated systemically), all patients' tumor tissue will be tested for expression of PD-L1, as determined by IHC, using a laboratory developed assay performed during Screening. Under amendment 06, the first 32 patients whose tumors express PD-L1, have non-squamous NSCLC, and have received at least two prior lines of systemic therapy are eligible for treatment with MK-3475 at 10 mg/kg Q3W. Under Amendment 07, 250 additional previously-treated patients for NSCLC with at least one prior line of systemic therapy whose tumors express PD-L1 will be randomized 3:2, manually by the Sponsor based on a computer-generated allocation schedule, to either 10 mg/kg Q3W or 10 mg/kg Q2W of MK-3475. These patients in F-2 may be stratified by either weak or strong PD-L1 expression level. Enrollment of patients with weakly positive tumor expression of PD-L1 will be limited to approximately 50% of the Q2W and Q3W patient cohorts. Additionally, 40 patients who are PD-L1 negative and have received at least two prior lines of systemic therapy for NSCLC will be eligible to receive MK-3475 at 10 mg/kg Q2W. An analytically validated assay PD-1L IHC assay will be used to determine the PD-L1 status of FFPE tumor samples.

Enrollment into the F-1 and F-2 cohorts will occur concurrently.

1.6 DOSAGE/DOSAGE FORM, ROUTE, AND DOSE REGIMEN

MK-3475 will be administered as a 30 minute IV infusion, with a window of -5 and +10 minutes (except as indicated in Part A-2). Study therapy for patients in all study parts will continue until disease progression or unacceptable toxicity. However in the

event of a confirmed complete response (CR), it is at the discretion of the investigator to keep a patient on study treatment or to discontinue study treatment based on the following guidelines. This decision will be based on the clinical judgment of a patient's overall clinical condition, including performance status, clinical symptoms, and laboratory data. Patients who have a confirmed complete response by two scans ≥4 weeks apart and who have been on MK-3475 treatment for at least 6 months may discontinue MK-3475 treatment at the discretion of the investigator after receiving at least two doses beyond the initial determination of CR. MK-3475 may be resumed (Second Course treatment) upon disease recurrence in these patients. See Section 3.2.5.4.13 for details regarding follow up for CR patients who discontinue treatment with MK-3475, and section 3.2.5.4.14 for details regarding eligibility for second course treatment and Section 1.7 (Study Flow Chart) for details on procedures.

Part A will consist of a dose escalation followed by additional analysis of PK and pharmacodynamic characteristics. Three dose levels of MK-3475 will be evaluated in the dose escalation: 1 mg/kg; 3 mg/kg; and 10 mg/kg. To ascertain detailed PK analysis, the interval between the first and second dose in the Part A dose escalation will be 28 days. In subsequent cycles the dosing interval will be 14 days.

Additional patients will be enrolled in Part A to further explore PK characteristics. In Part A-1, six patients may be enrolled at the MTD up to 10 mg/kg, with a dosing interval every 2 weeks (Q2W). In Part A-2, 12 patients may be enrolled to further define PK characteristics with a dosing interval of every 3 weeks (Q3W) beginning with Cycle 2. In this cohort, lower doses (below 1 mg/kg) will be tested in order to explore relationship between PK and pharmacodynamics of MK-3475. PK and pharmacodynamic sample collection times for these 12 patients are presented in the table Details of Sampling for Pharmacokinetics and Pharmacodynamics for Part A-2 in Section 1.7. These patients will be enrolled following completion of enrollment in Part A-1. These patients will receive escalating doses in Cycle 1 as indicated in Table 1-2 and Table 1-3 below. Patients who do not complete Cycle 1 in Part A-2 may be replaced.

Table 1-2

Part A-2 Dose Titration

	N	Day 1	Day 8	Day 22[1]	C2 and beyond[2]
Cohort 1	3	0.005 mg/kg[3]	0.3 mg/kg[3]	2.0 mg/kg	2.0 mg/kg
Cohort 2	3	0.02 mg/kg[3]	0.3 mg/kg[3]	2.0 mg/kg	2.0 mg/kg
Cohort 3	6	0.06 mg/kg[3]	1.0 mg/kg	10.0 mg/kg	10.0 mg/kg

Patients will be randomly assigned to each cohort by the Sponsor.
1 Day 22 sample = predose for Cycle 2/Day 1 for patients continuing in the study.
2 Dosing schedule C2 and beyond is Q3W.
3 Administered via IV push.

Table 1-3

Part A-2 Titration, Dose Matrix View

	Dose (mg/kg)						
Cohort	**0.005**	**0.02**	**0.06**	**0.3**	**1.0**	**2.0**	**10.0**
1 (n=3)	X			X		x	
2 (n=3)		x		X		x	
3 (n=6)			X		x		x
Total n[1]	3	3	3	6	6	6	6

Patients will be randomly assigned to each cohort.
1 Total is at a given dose across all cohorts and times.

In Part B, MK-3475 will be administered at the preliminary RP2D(s) as per Section 1.5. For patients who consent under protocol Amendment 001-02, dosing will be repeated Q2W at 10 mg/kg. For patients consented under protocol Amendments 001-03, 001-04, 001-05, 001-06, or following approval of the administrative memo dated 06-Jan-2012, dosing in Part B will be repeated Q3W at 2 mg/kg and 10 mg/kg. Patients who consent under protocol Amendment 07 will be randomized 1:1, manually by the Sponsor, to 10 mg/kg MK-3475 at either Q2W or Q3W, using an allocation schedule generated in-house. Patients who initiate therapy on the 2 week schedule will not switch to the 3 week schedule unless there is an adverse experience warranting such a reduction in schedule.

In Part C, MK-3475 will be administered at preliminary RP2D, 10 mg/kg. Dosing in Part C will be repeated Q3W.

In Part D, MK-3475 will be administered at either 2 or 10 mg/kg. Dosing in Part D will be repeated Q3W. A total of 88 patients will be randomized 1:1, manually by the

Sponsor, to either 2 mg/kg or 10 mg/kg MK-3475 using an allocation schedule generated in-house. Once a patient is eligible for treatment, the Sponsor will inform the site of the appropriate dose to administer.

Part F will be split between treatment naïve patients (F-1) and patients with at least 1 prior systemic regimen (F-2). Once the appropriate line of therapy is identified, treatment-naive patients whose tumors express PD-L1 will be randomized 1:1 in F-1, manually by the Sponsor based on a computer-generated allocation schedule, to either 10 mg/kg Q2W or 10 mg/kg Q3W. Under Amendment 07, 40 previously-treated patients with at least two prior lines of therapy whose tumors do not express PD-L1 will receive 10 mg/kg Q2W in F-2. All other patients in F-2 will randomized 3:2 manually by the Sponsor, to either 10 mg/kg Q3W or 10 mg/kg Q2W of MK-3475 using an allocation schedule generated in-house.

Upon approval of Amendment 07, investigators have the option to provide patients with 10 mg/kg Q3W dosing if they enrolled in F-1 under Amendment 06 at 2 mg/kg Q3W. Although investigators are encouraged to permit patients with NSCLC assigned 2mg/kg Q3W to remain on that dose if progression of cancer has not been identified. Patients with NSCLC assigned to 2 mg/kg under amendment 06, who are treated with 2 mg/kg Q3W until disease progression, may be treated at 10 mg/kg Q3W upon confirmation of disease progression by irRC, assuming that the patient is clinically stable as described in Section 2.4.1, if the patient and investigator agree.

Listed below are the MK-3475 treatment groups in Part F AM07 and AM08:

F-1:

- NSCLC: Treatment naïve (first-line treatment – 88 total patients):
  - 10 mg/kg MK-3475 Q2W, PD-L1 tumor expression (44 patients)
  - 10 mg/kg MK-3475 Q3W, PD-L1 tumor expression (44 patients)

F-2:

- NSCLC: 1 or more Prior Systemic Treatments (250 total patients):
  - 10 mg/kg, MK-3475 Q3W, PD-L1 tumor expression (150 patients)
  - 10 mg/kg, MK-3475 Q2W, PD-L1 tumor expression (100 patients)
- NSCLC : 2 or more Prior Systemic Treatments (72 total patients)
  - 10 mg/kg MK-3475 Q2W, no PD-L1 tumor expression (40 patients)

Dose escalation in individual patients will not be permitted in this study, except where indicated in Part A-2, or patients enrolled in Part F-1 under amendment 06 who were

randomized to 2mg/kg Q3W of MK-3475 who experience confirmed disease progression at that dose.

1.7 STUDY FLOW CHART

Note: there are separate Flow Charts for Part A (A-1), Part A-2, Part B (Q2W and Q3W flow charts), Part C, Part D, and Part F.

Part A, Part A-1											
	Screening [1] (-28 to 1 days)	Cycle 1 (28 Days)							Cycle 2 and Additional Cycles (14 Days ± 2 Days)	Safety Follow-up [2] (30 Days ± 3 Days after last dose)	Follow Up Visits [26]
Cycle Day		1	2	3	8	15	22	29 [3]	1		
Visit Number	1	2	3	4	5	6	7	8	N		
Study Procedures											
Informed Consent [4]	X										
Informed Consent for Future Biomedical Research (optional)	X										
Inclusion/Exclusion Criteria	X										
Demographics/Medical History/ Prior Medications [5]	X										
Vital Signs/Weight [6]	X	X				X		X	X	X	
Physical Examination	X					X		X	X	X	
ECOG Performance Status	X							X	X	X	
12-Lead ECG [7]	X	X						X	X	X	
Review Adverse Events [8]		X			X	X	X	X	X	X	X
Review Concomitant Medications		X			X	X	X	X	X	X	

Part A, Part A-1 (cont)											
	Screening [1] (-28 to 1 days)	Cycle 1 (28 Days)							Cycle 2 and Additional Cycles (14 Days ± 2 Days)	Safety Follow-up [2] (30 Days ± 3 Days after last dose)	Follow Up Visits [26]
Cycle Day		1	2	3	8	15	22	29 [3]	1		
Visit Number	1	2	3	4	5	6	7	8	N		
Study Procedures											
CBC with Differential [9]	X					X		X	X	X	
Comprehensive Serum Chemistry Panel [9]	X					X		X	X	X	
Coagulation Parameters [10]	X									X	
Urinalysis [9]	X	X				X		X	X	X	
Pregnancy Test - Urine or Serum β-HCG [11]	X										
Lymphocyte Subtyping (FACS) [12]		X		X	X	X	X	X	X	X	
Thyroid Function [13]		X							X	X	
Immunoglobulins [14]		X						X	X	X	
Viral Antigen Recall Reactions [15]		X		X	X	X	X	X			
Cytokine/Chemokine Panel [16]		X							X		
Auto-Antibodies [17]		X							X	X	
Anti-MK-3475 Antibodies [18]		X							X	X	X
Proteomics in Blood [19]		X							X		
RNA Signature Profiling in Blood [19]		X							X		

Part A, Part A-1 (cont)

	Screening [1] (-28 to 1 days)	Cycle 1 (28 Days)							Cycle 2 and Additional Cycles (14 Days ± 2 Days)	Safety Follow-up [2] (30 Days ± 3 Days after last dose)	Follow Up Visits [26]
Cycle Day		1	2	3	8	15	22	29 [3]	1		
Visit Number	1	2	3	4	5	6	7	8	N		
Study Procedures											
Pharmacodynamics [20]		X	X		X			X	X	X	
Pharmacokinetics [20]		X	X	X	X	X	X	X	X	X	X
HIV, Hepatitis B and C [21]	X										
Blood for Future Biomedical Research [27] (optional)		X									
Efficacy Measurements											
Serum Tumor Markers (if appropriate) [22]	X								X	X	X
Tumor Imaging [23]	X								X	X	X
Drug Administration											
Study Drug Administration (30 minute infusion)		X							X		
Tumor Biopsies											
Archival Tumor Tissues [24]	X										
Newly Obtained Tumor Biopsies [25]	X								X		

1 Routine laboratory tests (serum chemistry; hematology) for screening should be performed within 10 days of enrollment.
2 The mandatory Safety Follow-Up visit should be conducted 30 days (±3 days) after the last dose of study therapy or before the initiation of a new treatment, whichever comes first. Patients who are discontinued from the study due to an unacceptable drug-related adverse event will be followed until the resolution of the adverse event (AE) to Grade 0-1 or stabilization or until beginning of a new therapy for their cancer, whichever occurs first.
3 Day 29 sample = predose for Cycle 2/Day 1 for patients continuing in the study.
4 Written consent must be obtained prior to performing any protocol specific procedure. Results of a test performed as part of routine clinical management are

acceptable in lieu of a screening test if performed within the specified time frame (e.g. within 28 days prior to Cycle 1, Day 1). Assign Baseline number when the study informed consent is signed.

5 Includes history of treatment for the primary diagnosis, including prior systemic, radiation treatment and surgical treatment. Date of last prior cancer treatment must be documented. Radiographic studies performed prior to study entry may be collected for review by the investigator. Report complete medication history for 30 days prior to the screening visit (Visit 1).

6 Vital signs to include temperature, pulse, respiratory rate and blood pressure. If a patient's baseline weight does not fluctuate by more than 10%, this weight can be used to calculate dose.

7 Electrocardiogram (12-lead ECG) should be performed at Screening, at the time of PK blood collection for PK (Cmax) within 30 minutes after the end of the first infusion of MK-3475, after infusion of MK-3475 in every other cycle (within 30 minutes after the end of infusion), and at the mandatory Safety Follow-up visit.

8 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. Study site should contact the patient mid-cycle to assess for potential irAEs.

9 See Appendix 6.1 for list of laboratory tests. Routine laboratory tests (e.g., CBC with differential; comprehensive serum chemistry panel; urinalysis) will be performed by the local study site laboratory or their contract laboratory. CBC, serum chemistry and urinalysis may be collected up to 48 hours prior to any Cycle "X", Day 1 dosing.

10 PT/INR and aPTT should be collected at Screening and at the mandatory Safety Follow-up Visit after discontinuation of study therapy. Coagulation parameters should be determined throughout the study when clinically indicated. PT/INR and aPTT will be analyzed by the local study site laboratory.

11 For women of reproductive potential, a urine 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. Women who have been amenorrheaic for <2 years and who have not had a hysterectomy and oophorectomy will only be considered not to be of reproductive potential if they have a documented FSH value in the postmenopausal range.

12 Cycle 1: predose; Days 3, 8, 15, 22 and 29; Cycle 2 and subsequently every other cycle in the first 12 months on study at predose; at the mandatory Safety Follow-Up Visit. FACS analysis of lymphocyte subpopulations will be performed in a central laboratory.

13 T3, FT4, TSH; at every cycle, and at the mandatory Safety Follow-Up Visit. Analysis of T3, FT4 and TSH will be performed by a central laboratory.

14 Analysis of IgG and IgM at predose of Cycle 1, on day 29 of Cycle 1, at predose every other cycle in first 12 months, approximately every 2 months thereafter, and at Safety Follow-Up Visit. Analysis will be performed by the local study site laboratory.

15 Cycle 1: predose; Days 3, 8, 15, 22 and 29. The analysis will be performed by a central laboratory.

16 Cycle 1: predose, 1 h +/- 30 minutes after end of infusion, and 6 hours (± 30 minutes) after start of infusion. Subsequently to be collected at predose approximately every month until 6 months of study therapy. Includes multi-analysis panels (MAPs) such as Cytokine MAPAv1.0 and MAPBv1.0, and OncologyMAPv1.0 from RulesBasedMedicine. Analysis of cytokines/chemokines will be performed by a central laboratory.

17 Collected at predose of Cycle 1 and Cycle 2, and then of every other cycle following Cycle 2. Include antinuclear antibodies; anti-DNA antibodies; antithyroglobulin antibodies; antimicrosomal antibodies; and anticardiolipin antibodies. When a blood sample is positive for antinuclear antibodies (i.e., titer of ≥40), it will be tested for antibodies against extractable nuclear antigens. Analysis will be performed by a central laboratory.

18 Blood for anti-MK-3475 antibodies should be collected within 24 hours before start of infusion in Cycle 1 and Cycle 2 within 24 hours before start of infusion in every other subsequent cycle, and at the mandatory Safety Follow-Up Visit. Every effort should be made to collect additional blood samples for anti-MK-3475 antibodies approximately every 2 months after the Safety Follow-Up Visit for up to 6 months from the last dose of MK-3475 or until start of a new anti-cancer therapy, whichever occurs first. Analysis will be performed by a central laboratory.

19 Blood collected at predose of Cycle 1 and every month at predose until 6 months of study therapy. Analysis will be performed by a central laboratory.
20 For timing refer to the following chart on Details of Sampling for Pharmacokinetics and Pharmacodynamics flow chart for timing. Procedures for collection of samples are described in the Procedures Manual.
21 Testing will be performed by the local laboratory at Screening. Include HCV RNA (qualitative), HBsAg, and HIV 1/2 antibodies.
22 Standard tumor markers (as appropriate for a given tumor type) will be collected within 14 days prior to Cycle 1/Day 1, and while on study approximately every 2 months in the first 12 months and approximately every 3 months thereafter. Analysis will be performed by the local study site laboratory where feasible. If not feasible, tests will be performed by a central laboratory.
23 Tumor imaging (either CT or MRI, with preference for CT; lung x-ray) will be performed within 30 days prior to enrollment, and while on study approximately every 2 months in the first 12 months and approximately every 3 months thereafter. The same imaging technique should be used in a patient throughout the study. After first documentation of response (CR or PR) imaging performed at the next regularly scheduled time point (e.g., 2 months later in the first 12 months of study therapy) will be used for response confirmation. In patients who have measurable disease, response status will be assessed by the study site and by a central imaging vendor. The process for collection of CT images and transmission to the central vendor for purpose of central response review is described in the Procedures Manual.
24 Collection of archival tumor tissue for purpose of biomarker analysis. Access to archival tumor tissue is highly desirable but not mandatory. Written patient consent is required for collection of archival tumor tissue. Specific instructions for tissue collection and shipment are provided in the Procedures Manual. If the subject signs the Future Biomedical Research (FBR) consent, any leftover tissue that would ordinarily be discarded at the end of the main study will be retained for FBR, again providing the patient has signed the FBR consent.
25 A newly obtained biopsy of a tumor lesion is desirable but not mandatory. Written patient consent is required for newly obtained biopsies. A baseline biopsy obtained for other purposes (i.e., not a PN001 study procedure), prior to signing consent, can be utilized if obtained within 60 days of first dose of MK-3475 (Cycle 1 Day 1). Newly obtained biopsies should be limited to readily accessible tumor lesions (e.g., skin; peripheral lymph nodes; lung, liver or internal lymph node metastases which can be readily accessed using CT guidance). If performed, a tissue cylinder should be obtained that has proper size for histological examination and biomarker analysis (e.g., IHC of PD-1, PD-L1, PD-L2; RNA signature profiling). (See specific guidance for minimum needle gauge in the procedures manual.) When feasible, another tumor biopsy should be taken approximately 2 months after start of study therapy, so tissue characteristics such as biomarkers can be compared to baseline. If feasible, the follow-up biopsy should be ideally taken from the same tumor lesion as the baseline biopsy. If the subject signs the Future Biomedical Research (FBR) consent, any leftover tissue that would ordinarily be discarded at the end of the main study will be retained for FBR, again providing the patient has signed the FBR consent.
26 Every effort should be made to collect blood samples for PK for up to 6 months after the last dose as per the guidelines in the "Details of Sampling for Pharmacokinetics and Pharmacodynamics" flow chart. Every effort should be made to collect blood samples for anti-MK-3475 antibodies for up to 6 months as per the guidelines in footnote 18. In patients who discontinue study therapy early without documented disease progression, every effort should be made to continue monitoring their disease status by radiologic imaging (1) for approximately 6 months without disease progression, (2) until start of a new anti-cancer treatment, (3) until documented disease progression, or (4) until death, whichever occurs first.
27 Informed consent for future biomedical research samples must be obtained before the DNA sample. DNA sample for analysis should be obtained predose, on Day 1 (or with the next scheduled blood draw), as the last sample drawn, on randomized subjects only, or at a later date as soon as the informed consent is obtained. This sample should only be taken once from each subject

Part A-2																	
	Screening [1] (-28 to 1 days)	Cycle 1							Cycle 2						Cycle 3 and Additional Cycles (21 Days ± 2 Days)	Safety Follow-up [2] (30 Days ± 3 Days after last dose)	Follow Up Visits [26]
Cycle Day		1	2	3	5	8	15	22 [3]	1	2	3	8	15	22 [3]	1		
Study Procedures																	
Informed Consent [4]	X																
Informed Consent for Future Biomedical Research (optional)	X																
Inclusion/Exclusion Criteria	X																
Demographics/Medical History/ Prior Medications [5]	X																
Vital Signs/Weight [6]	X	X					X		X						X	X	
Physical Examination	X						X		X						X	X	
ECOG Performance Status	X								X						X	X	
12-Lead ECG [7]	X	X							X						X	X	
Review Adverse Events [8]		X				X	X	X	X						X	X	
Review Concomitant Medications		X				X	X	X	X						X	X	
CBC with Differential [9]	X						X		X						X	X	
Comprehensive Serum Chemistry Panel [9]	X						X		X						X	X	
Coagulation Parameters [10]	X															X	
Urinalysis [9]	X	X					X		X						X	X	

Part A-2 (cont)

	Screening [1] (-28 to 1 days)	Cycle 1						Cycle 2							Cycle 3 and Additional Cycles (21 Days ± 2 Days)	Safety Follow-up [2] (30 Days ± 3 Days after last dose)	Follow Up Visits [26]
Cycle Day		1	2	3	5	8	15	22 [3]	1	2	3	8	15	22 [3]	1		
Study Procedures																	
Pregnancy Test - Urine or Serum β-HCG [11]	X																
Lymphocyte Subtyping (FACS) [12]		X		X		X	X	X	X						X	X	
Thyroid Function [13]		X							X						X	X	
Immunoglobulins [14]		X						X	X						X	X	
Cytokine/Chemokine Panel [15]		X							X						X		
Auto-Antibodies [16]		X							X						X	X	
Anti-MK-3475 Antibodies [17]		X							X						X	X	X
Proteomics in Blood [18]		X							X						X		
RNA Signature Profiling in Blood [18]		X							X						X		
Pharmacodynamics [19]		X	X			X			X	X					X		
Pharmacokinetics [19]		X	X	X	X	X	X	X	X		X	X	X	X	X	X	X
HIV, Hepatitis B and C [20]	X																
Blood for Future Biomedical Research[27] (optional)		X															

Part A-2 (cont)

	Screening [1] (-28 to 1 days)	Cycle 1						Cycle 2							Cycle 3 and Additional Cycles (21 Days ± 2 Days)	Safety Follow-up [2] (30 Days ± 3 Days after last dose)	Follow Up Visits [26]
Cycle Day		1	2	3	5	8	15	22 [3]	1	2	3	8	15	22 [3]	1		
Efficacy Measurements																	
Serum Tumor Markers (if appropriate) [21]	X														X	X	X
Tumor Imaging [22]	X														X[22]	X	X
Drug Administration																	
Study Drug Administration[23]		X				X			X						X		
Tumor Biopsies																	
Archival Tumor Tissues [24]	X																
Newly Obtained Tumor Biopsies [25]	X														X[24]		

1 Routine laboratory tests (serum chemistry; hematology) for screening should be performed within 10 days of enrollment.
2 The mandatory Safety Follow-Up visit should be conducted 30 days (±3 days) after the last dose of study therapy or before the initiation of a new treatment, whichever comes first. Patients who are discontinued from the study due to an unacceptable drug-related adverse event will be followed until the resolution of the adverse event (AE) to Grade 0-1 or stabilization or until beginning of a new therapy for their cancer, whichever occurs first.
3 Day 22 sample = predose for Cycle 2/Day 1 or Cycle 3/Day 1 for patients continuing in the study.
4 Written consent must be obtained prior to performing any protocol specific procedure. Results of a test performed as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame (e.g. within 28 days prior to Cycle 1, Day 1). Assign Baseline number when the study informed consent is signed.
5 Includes history of treatment for the primary diagnosis, including prior systemic, radiation treatment and surgical treatment. Date of last prior cancer treatment must be documented. Radiographic studies performed prior to study entry may be collected for review by the investigator. Report complete medication history for 30 days prior to the screening visit (Visit 1).
6 Vital signs to include temperature, pulse, respiratory rate and blood pressure. If a patient's baseline weight does not fluctuate by more than 10%, this weight can be used to calculate dose.
7 Electrocardiogram (12-lead ECG) should be performed at Screening, at the time of PK blood collection for PK (Cmax) within 30 minutes after the end of the

first administration of MK-3475, after infusion of MK-3475 in every other cycle (within 30 minutes after the end of infusion), and at the mandatory Safety Follow-up visit.

8 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. Study site should contact the patient mid-cycle (approximately 10 days post-dose) to assess for potential irAEs.

9 See Appendix 6.1 for list of laboratory tests. Routine laboratory tests (e.g., CBC with differential; comprehensive serum chemistry panel; urinalysis) will be performed by the local study site laboratory or their contract laboratory. CBC, serum chemistry and urinalysis may be collected up to 48 hours prior to any Cycle "X", Day 1 dosing.

10 PT/INR and aPTT should be collected at Screening and at the mandatory Safety Follow-up Visit after discontinuation of study therapy. Coagulation parameters should be determined throughout the study when clinically indicated. PT/INR and aPTT will be analyzed by the local study site laboratory.

11 For women of reproductive potential, a urine 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. Women who have been amenorrheaic for <2 years and who have not had a hysterectomy and oophorectomy will only be considered not to be of reproductive potential if they have a documented FSH value in the postmenopausal range.

12 Cycle 1: predose; Days 3, 8, 15, and 22; Cycle 2 and subsequently every other cycle in the first 12 months on study at predose; at the mandatory Safety Follow-Up Visit. FACS analysis of lymphocyte subpopulations will be performed in a central laboratory.

13 T3, FT4, TSH; at every cycle, and at the mandatory Safety Follow-Up Visit. Analysis of T3, FT4 and TSH will be performed by a central laboratory.

14 Analysis of IgG and IgM at predose of Cycle 1, on day 22 of Cycle 1, at predose every other cycle in first 12 months, approximately every 2 months thereafter, and at Safety Follow-Up Visit. Analysis will be performed by the local study site laboratory.

15 Cycle 1: predose, 1 h +/- 30 minutes after end of study drug administration, and 6 hours (± 30 minutes) after start of study drug administration. Subsequently to be collected at predose approximately every month until 6 months of study therapy. Includes multi-analysis panels (MAPs) such as Cytokine MAPAv1.0 and MAPBv1.0, and OncologyMAPv1.0 from RulesBasedMedicine. Analysis of cytokines/chemokines will be performed by a central laboratory.

16 Collected at predose of Cycle 1 and Cycle 2, and then of every other cycle following Cycle 2. Include antinuclear antibodies; anti-DNA antibodies; antithyroglobulin antibodies; antimicrosomal antibodies; and anticardiolipin antibodies. When a blood sample is positive for antinuclear antibodies (i.e., titer of ≥40), it will be tested for antibodies against extractable nuclear antigens. Analysis will be performed by a central laboratory.

17 Blood for anti-MK-3475 antibodies should be collected within 24 hours before start of study drug administration in Cycle 1 and Cycle 2 within 24 hours before start of infusion in every other subsequent cycle, and at the mandatory Safety Follow-Up Visit. Every effort should be made to collect additional blood samples for anti-MK-3475 antibodies approximately every 2 months after the Safety Follow-Up Visit for up to 6 months from the last dose of MK-3475 or until start of a new anti-cancer therapy, whichever occurs first. Analysis will be performed by a central laboratory.

18 Blood collected at predose of Cycle 1 and every month at predose until 6 months of study therapy. Analysis will be performed by a central laboratory.

19 For timing refer to the following chart on Details of Sampling for Pharmacokinetics and Pharmacodynamics for Part A-2 flow chart for timing. Procedures for collection of samples are described in the Procedures Manual.

20 Testing will be performed by the local laboratory at Screening. Include HCV RNA (qualitative), HBsAg, and HIV 1/2 antibodies.

21 Standard tumor markers (as appropriate for a given tumor type) will be collected within 14 days prior to Cycle 1/Day 1, and while on study approximately every 2 months in the first 12 months and approximately every 3 months thereafter. Analysis will be performed by the local study site laboratory where feasible. If not feasible, tests will be performed by a central laboratory.

22 Tumor imaging (either CT or MRI, with preference for CT; lung x-ray) will be performed within 30 days prior to enrollment, and while on study approximately every 2 months in the first 12 months and approximately every 3 months thereafter. The same imaging technique should be used in a patient throughout the study. After first documentation of response (CR or PR) imaging performed at the next regularly scheduled time point (e.g., 2 months later in the first 12 months of study therapy) will be used for response confirmation. In patients who have measurable disease, response status will be assessed by the study site and by a central imaging vendor. The process for collection of CT images and transmission to the central vendor for purpose of central response review is described in the Procedures Manual.

23 Doses less than 1.0 mg/kg will be administered via IV push. Doses of 1.0 mg/kg and greater will be administered via infusion. Specific instructions for both administration procedures are provided in the Procedures Manual.

24 Collection of archival tumor tissue for purpose of biomarker analysis. Access to archival tumor tissue is highly desirable but not mandatory. Written patient consent is required for collection of archival tumor tissue. Specific instructions for tissue collection and shipment are provided in the Procedures Manual. If the subject signs the Future Biomedical Research (FBR) consent, any leftover tissue that would ordinarily be discarded at the end of the main study will be retained for FBR, again providing the patient has signed the FBR consent.

25 A newly obtained biopsy of a tumor lesion is desirable but not mandatory. Written patient consent is required for newly obtained biopsies. A baseline biopsy obtained for other purposes (i.e., not a PN001 study procedure), prior to signing consent, can be utilized if obtained within 60 days of first dose of MK-3475 (Cycle 1 Day 1). Newly obtained biopsies should be limited to readily accessible tumor lesions (e.g., skin; peripheral lymph nodes; lung, liver or internal lymph node metastases which can be readily accessed using CT guidance). If performed, a tissue cylinder should be obtained that has proper size for histological examination and biomarker analysis (e.g., IHC of PD-1, PD-L1, PD-L2; RNA signature profiling). (See specific guidance for minimum needle gauge in the Procedures Manual.) When feasible, another tumor biopsy should be taken approximately 2 months after start of study therapy, so tissue characteristics such as biomarkers can be compared to baseline. If feasible, the follow-up biopsy should be ideally taken from the same tumor lesion as the baseline biopsy. If the subject signs the Future Biomedical Research (FBR) consent, any leftover tissue that would ordinarily be discarded at the end of the main study will be retained for FBR, again providing the patient has signed the FBR consent.

26 Every effort should be made to collect blood samples for PK for up to 6 months after the last dose as per the guidelines in the "Details of Sampling for Pharmacokinetics and Pharmacodynamics" flow chart. Every effort should be made to collect blood samples for anti-MK-3475 antibodies for up to 6 months as per the guidelines in footnote 17. In patients who discontinue study therapy early without documented disease progression, every effort should be made to continue monitoring their disease status by radiologic imaging (1) for approximately 6 months without disease progression, (2) until start of a new anti-cancer treatment, (3) until documented disease progression, or (4) until death, whichever occurs first.

27 Informed consent for future biomedical research samples must be obtained before the DNA sample. DNA sample for analysis should be obtained predose, on Day 1 (or with the next scheduled blood draw), as the last sample drawn, on randomized subjects only, or at a later date as soon as the informed consent is obtained. This sample should only be taken once from each subject.

Details of Sampling for Pharmacokinetics and Pharmacodynamics for Part A and Part A-1

	Cycle 1 (28 Days)									Cycle 2 and Additional Cycles (14 Days ± 2 Days)		Safety Follow-Up Visit (30 Days ± 3 Days after last dose)	Follow -Up Visits
Cycle Day	1			2	3	8	15	22	29	1			
	Predose	Postdose								Predose	Postdose		
Time Points	-60 min to 0 h	End infusion to +30 min[1]		24h[2]	48h[2]					-60 min to 0 h	End infusion to 30 min[2]		
Pharmacokinetics	X	X	X	X	X	X	X	X	X[3]	X[4]	X[4]	X[6]	X[7]
Pharmacodynamics: PD-1 Receptor Occupancy Assay	X			X		X			X[3]	X[5]		X[6]	
Pharmacodynamics: PD-1 Target Modulation Assay	X			X		X			X[3]	X[5]		X[6]	

Please note: Actual drug dosing and PK/pharmacodynamic sampling times have to be documented by the sites and will be captured in the database.

1 Sample collection must be from opposite arm to that used for study drug infusion. If drug was administered via a central venous catheter, sample collection for PK should be from a different site.
2 Window: ±2 hours.
3 Day 29 sample = predose for Cycle 2/Day 1 for patients continuing in the study.
4 Cycle 2 and subsequently every other cycle during the first 12 months of study therapy.
5 Cycle 2 and subsequently every 4th cycle during the first 12 months of study therapy.
6 PK and both pharmacodynamic assays should be performed at the mandatory Safety Follow-Up Visit.
7 Every effort should be made to collect additional PK samples every 4-8 weeks after the Safety Follow-Up Visit for up to 6 months from the last dose of MK-3475 or until start of a new anti-cancer therapy, whichever occurs first.

Details of Sampling for Pharmacokinetics and Pharmacodynamics for Part A-2

	-28 to 1 days	Cycle 1 (21 Days)										Cycle 2 (21 Days)							C3 and on (21 Days ± 2 Days)	Safety Follow-Up Visit (30 Days ± 3 Days after last dose)	Follow-Up Visits
Cycle Day		1	1	1	2	3	5	8	8	15	22	1	1	2	3	8	15	22	1		
Time Points		Pre	Post[3]	6 h[4]	24 h[4]	48 h[4]		Pre	Post			Pre	Post	24 h[4]							
Pharmacokinetics		X[1]	X[2]	X	X	X	X	X[1]	X[2]	X	X[5]	X[1]	X[2]		X	X	X	X[5]	X[6]	X[8]	X[9]
Pharmacodynamics: PD-1 Target Modulation Assay	X[10]	X[1]			X			X[1]				X[1]							X[7]	X[8]	
Pharmacodynamics: PD-1 Receptor Occupancy Assay		X[1]			X			X[1]				X[1]		X		X			X[7]	X[8]	

Please note: Actual drug dosing and PK/pharmacodynamic sampling times have to be documented by the sites and will be captured in the database.

1 Predose collection should be within 60 minutes of dosing (hour 0) each cycle PK is collected.
2 Postdose collection should be within 30 minutes of the end of study drug administration each cycle PK is collected.
3 Sample collection must be from opposite arm to that used for study drug administration/infusion. If drug was administered via a central venous catheter, sample collection for PK should be from a different site.
4 Window: ±2 hours.
5 Day 22 sample = predose for next cycle/Day 1 for patients continuing in the study.

6	Cycle 3 and subsequently every other cycle during the first 12 months of study therapy. Pre and Post dose collections.
7	Cycle 3 and subsequently every 4th cycle during the first 12 months of study therapy. Pre dose collections.
8	PK and pharmacodynamic assays should be performed at the mandatory Safety Follow-Up Visit.
9	Every effort should be made to collect additional PK samples every 4-8 weeks after the Safety Follow-Up Visit for up to 6 months from the last dose of MK-3475 or until start of a new anti-cancer therapy, whichever occurs first.
10	Two separate baseline blood draws should be performed during the screening period. The samples should be collected at least 1 day apart from each other and from the first dose (Cycle 1, Day 1).

Part B: 2 Week Schedule

	Screening [1] (-28 to 1 days)	Week/Cycle (14 Days ± 2 Days)													Cycle 14, 15, etc (14 Days ± 2 Days)
Week (approximate)		0	2	4	6	8	10	12	14	16	18	20	22	24	N
Cycle		1	2	3	4	5	6	7	8	9	10	11	12	13	N
Study Procedures															
Informed Consent [2]	X														
Informed Consent for Future Biomedical Research (optional)	X														
Inclusion/Exclusion Criteria	X														
Demographics/Medical History/ Prior Medications [3]	X														
Vital Signs/Weight [4]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECOG Performance Status	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-Lead ECG [5]	X	X								X					
Review Adverse Events [6]		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Review Concomitant Medications		X	X	X	X	X	X	X	X	X	X	X	X	X	X
CBC with Differential [7]	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Comprehensive Serum Chemistry Panel [7]	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Coagulation Parameters [8]	X														
Urinalysis [7]	X	X				X				X				X	X

Part B: 2 Week Schedule (cont)															
	Screening [1] (-28 to 1 days)	Week/Cycle (14 Days ± 2 Days)													Cycle 14, 15, etc (14 Days ± 2 Days)
Week (approximate)		0	2	4	6	8	10	12	14	16	18	20	22	24	N
Cycle		1	2	3	4	5	6	7	8	9	10	11	12	13	N
Study Procedures															
Pregnancy Test - Urine or Serum β-HCG [9]	X														
Thyroid Function [10]		X	X		X		X		X		X		X		X
Immunoglobulins [11]		X	X		X		X		X		X		X		X
Auto-Antibodies [12]		X	X		X		X		X		X		X		X
Anti-MK-3475 Antibodies [13]		X		X				X						X	X
Pharmacokinetics [14]		X		X				X						X	X
Lymphocyte Subtyping (FACS) [15]		X	X	X	X	X									
HIV, Hepatitis B and C [16]	X														
Proteomics and RNA Signature Profiling in Blood [17]		X	X	X		X		X							
BRAF Testing[22]	X														
Blood for Future Biomedical Research[23](optional)		X													
Human leukocyte antigen (HLA)[24]		X													

Part B: 2 Week Schedule (cont)

	Screening [1] (-28 to 1 days)	Week/Cycle (14 Days ± 2 Days)													Cycle 14, 15, etc (14 Days ± 2 Days)
Week (approximate)		0	2	4	6	8	10	12	14	16	18	20	22	24	N
Cycle		1	2	3	4	5	6	7	8	9	10	11	12	13	N
Efficacy Measurements															
Tumor Imaging [18, 19]	X							X		X[18]				X	X
Drug Administration															
Study Drug Administration (30 minute infusion)		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Tumor Biopsies															
Newly Obtained Tumor Biopsies [20]	X							X[20]						X[20]	
Archival Tumor Tissues [21]	X														

1 Routine laboratory tests (serum chemistry; hematology) for screening should be performed within 10 days of enrollment.
2 Written consent must be obtained prior to performing any protocol specific procedure. Results of a test performed as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame (e.g. within 28 days prior to Cycle 1, Day 1). Assign Baseline number when the study informed consent is signed.
3 Includes history of treatment for the primary diagnosis, including prior systemic, radiation treatment and surgical treatment, and best response to prior systemic treatments. Date of last prior cancer treatment must be documented. Radiographic studies performed prior to study entry may be collected for review by the investigator. Report complete medication history for 30 days prior to the screening visit (Visit 1).
4 Vital signs to include temperature, pulse, respiratory rate and blood pressure. If a patient's baseline weight does not fluctuate by more than 10%, this weight can be used to calculate dose.
5 Electrocardiogram (12-lead ECG) should be performed at Screening, at the time of PK blood collection for PK (Cmax) within 30 minutes after the end of the first infusion of MK-3475 (Cycle 1), Cycle 9 and at the mandatory Safety Follow-up visit. Triplicate 12-lead ECG measurements should be collected at the pre-dose and post dose at Cycle 1, and only post dose at Cycle 9 (Cmax). Only 1 measurement is required at Screening.

6 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. Study site should contact the patient mid-cycle (approximately 7 days post-dose) to assess for potential irAEs.
7 See Appendix 6.1 for list of laboratory tests. Routine laboratory tests (e.g., CBC with differential; comprehensive serum chemistry panel; urinalysis) will be performed by the local study site laboratory or their contract laboratory. Following Week 24, urinalysis should be performed every 8 weeks. CBC, serum chemistry and urinalysis may be collected up to 48 hours prior to any Cycle "X", Day 1 dosing.
8 PT/INR and aPTT should be collected at Screening and at the mandatory Safety Follow-up Visit after discontinuation of study therapy. Coagulation parameters should be determined throughout the study when clinically indicated. PT/INR and aPTT will be analyzed by the local study site laboratory.
9 For women of reproductive potential, a urine 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. Women with amenorrhea for <2 years and who have not had a hysterectomy and oophorectomy will only be considered not to be of reproductive potential if they have a documented FSH value in the postmenopausal range.
10 Analysis of T3, FT4 and TSH will be performed by a central laboratory. Following Cycle 2, testing will be performed every other cycle.
11 Analysis of IgG and IgM will be performed by the local study site laboratory. Following Cycle 2, testing will be performed every other cycle.
12 Collected prior to dosing in Cycle 1 and Cycle 2, and then in every other subsequent cycle. Include antinuclear antibodies; anti-DNA antibodies; antithyroglobulin antibodies; antimicrosomal antibodies; and anticardiolipin antibodies. When a blood sample is positive for antinuclear antibodies (i.e., titer of ≥40), it will be tested for antibodies against extractable nuclear antigens. Analysis will be performed by a central laboratory.
13 Blood for anti-MK-3475 antibodies should be collected in Cycles 1, 3, 7 and 13. Subsequently, testing should be performed approximately every 12 weeks for the first 12 months on the study, and approximately every 6 months thereafter. All samples should be drawn within 24 hours before infusion of MK-3475 and at the same time as blood collection for C_{trough}
14 Procedures for collection of samples are described in the Procedures Manual. Peak and trough samples will be collected at Cycles 1 and 3. A trough sample should be collected at Cycle 7. Subsequently, trough samples should be collected approximately every 12 weeks for the first 12 months on the study, then approximately every 6 months thereafter. All trough samples should be drawn within 24 hours before infusion of MK-3475 and at the same time as blood collection for anti-MK-3475 antibodies. The two peak samples in Cycles 1 and 3 should be drawn within 30 minutes after the end of the infusion.
15 Collected before start of infusion. FACS analysis of lymphocyte subpopulations will be performed in a central laboratory.
16 Testing will be performed by the local laboratory at Screening. Include HCV RNA (qualitative), HBsAg, and HIV 1/2 antibodies.
17 Blood collected at predose of Cycle 1 and before infusion of MK-3475 in Cycles 2, 3, 5 and 7. Analysis will be performed by a central laboratory.

18 Tumor imaging (either CT or MRI, with strong preference for CT; lung x-ray) will be performed within 30 days prior to enrollment. The same imaging technique has to be used in a patient throughout the study. After first documentation of response or progression, repeat imaging is required approximately 4 weeks later for confirmation, as per immune related response criteria (irRC) guidelines (see Appendix 6.5) (see Section 2.4.1). Tumor imaging will be performed approximately every 12 weeks (or whenever clinically indicated) while the patient remains on study therapy regardless of Cycle/Day. Response status will be assessed by the study site and by a central imaging vendor. The process for collection of CT images and transmission to the central vendor for purpose of central response review is described in the Procedures Manual. Refer to Section 3.3.1.3 of the protocol for additional information. If a tumor biopsy was obtained from a target lesion during eligibility assessment, it is preferred to obtain a new baseline scan.

19 Ipilimumab-refractory patients must send pre-trial scans confirming investigator-determined PD (according to irRC) to the central imaging vendor. Details are provided in the Procedures Manual.

20 A newly obtained biopsy of at least one tumor lesion is mandatory at baseline (prior to Cycle 1/Day 1). A baseline biopsy obtained for other purposes (i.e., not a PN001 study procedure), prior to signing consent, can be utilized if obtained within 60 days of first dose of MK-3475 (Cycle 1 Day 1). Additional biopsy samples approximately at Week 12, Week 24, and at disease progression are highly desirable. Further biopsy samples may be obtained at time points other than those specified here if deemed appropriate by the investigator. When it is feasible, more than one biopsy should be performed at a given time point (e.g., from the same lesion or from different lesions). The tissue sample should have proper size to enable all planned biomarker analyses (e.g., IHC of PD-L1, PD-1, PD-L2; RNA signature profiling), but does not artificially decrease the longest diameter of the lesion. Fine needle aspiration will not be acceptable. The biopsy techniques allowed in the study include tru cut core biopsies or surgical biopsies. Study sites should use the same biopsy techniques in this study as they routinely use for a given tumor lesion/location. Biopsy of lesions on study should be limited to non-target lesions or new lesions if their pathologic etiology is ambiguous. Detailed instructions for tissue collection, processing and shipment are provided in the Procedures Manual. If the subject signs the Future Biomedical Research (FBR) consent, any leftover tissue that would ordinarily be discarded at the end of the main study will be retained for FBR, again providing the patient has signed the FBR consent.

21 Collection of archival tumor tissue for purpose of biomarker analysis is strongly encouraged. For patients enrolled with Amendment 07 and 08, collection of archival tumor tissue is mandatory and samples from fine needle aspiration will not be acceptable. An archival specimen is mandatory to be submitted within 3 weeks from the day a patient signs informed consent. Patients who do not have an archival specimen can only be enrolled after discussion with the sponsor. Specific instructions for tissue collection and shipment are provided in the Procedures Manual. If the subject signs the Future Biomedical Research (FBR) consent, any leftover tissue that would ordinarily be discarded at the end of the main study will be retained for FBR, again providing the patient has signed the FBR consent.

22 Required at screening for patients without documented BRAF status. Analysis will be performed by a central laboratory.

23 Informed consent for future biomedical research samples must be obtained before the DNA sample. DNA sample for analysis should be obtained predose, on Day 1 (or with the next scheduled blood draw), as the last sample drawn, on randomized subjects only, or at a later date as soon as the informed consent is obtained. This sample should only be taken once from each subject.

24 Collected in patients enrolled with Amendment 07 and 08.

Part B: 3 Week Schedule															
	Screening [1] (-28 to 1 days)	Week/Cycle (21 Days ± 2 Days)													Cycle 14, 15, etc (21 Days ± 2 Days)
Week (approximate)		0	3	6	9	12	15	18	21	24	27	30	33	36	N
Cycle		1	2	3	4	5	6	7	8	9	10	11	12	13	N
Study Procedures															
Informed Consent [2]	X														
Informed Consent for Future Biomedical Research (optional)	X														
Inclusion/Exclusion Criteria	X														
Demographics/Medical History/ Prior Medications [3]	X														
Vital Signs/Weight [4]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECOG Performance Status	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-Lead ECG [5]	X	X					X								
Review Adverse Events [6]		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Review Concomitant Medications		X	X	X	X	X	X	X	X	X	X	X	X	X	X
CBC with Differential [7]	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Comprehensive Serum Chemistry Panel [7]	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Coagulation Parameters [8]	X														
Urinalysis [7]	X	X			X			X			X			X	X

Part B: 3 Week Schedule (cont)															
	Screening [1] (-28 to 1 days)	Week/Cycle (21 Days ± 2 Days)													Cycle 14, 15, etc (21 Days ± 2 Days)
Week (approximate)		0	3	6	9	12	15	18	21	24	27	30	33	36	N
Cycle		1	2	3	4	5	6	7	8	9	10	11	12	13	N
Study Procedures															
Pregnancy Test - Urine or Serum β-HCG [9]	X														
Thyroid Function [10]		X	X		X		X		X		X		X		X[10]
Immunoglobulins [11]		X	X		X		X		X		X		X		X[11]
Auto-Antibodies [12]		X	X		X		X		X		X		X		X[12]
Anti-MK-3475 Antibodies [13]		X	X			X				X				X	X[13]
Pharmacokinetics [14]		X	X			X				X				X	X[14]
Lymphocyte Subtyping (FACS) [15]		X	X	X	X										
HIV, Hepatitis B and C [16]	X														
Proteomics and RNA Signature Profiling in Blood [17]		X	X	X		X		X							
BRAF Testing[22]	X														
Human leukocyte antigen (HLA)[24]		X													
Blood for Future Biomedical Research[23](optional)		X													
Efficacy Measurements															
Tumor Imaging [18]	X					X[18]				X[18]				X[18]	X[18]

Part B: 3 Week Schedule (cont)

	Screening [1] (-28 to 1 days)	Week/Cycle (21 Days ± 2 Days)													Cycle 14, 15, etc (21 Days ± 2 Days)
Week (approximate)		0	3	6	9	12	15	18	21	24	27	30	33	36	N
Cycle		1	2	3	4	5	6	7	8	9	10	11	12	13	N
Drug Administration															
Study Drug Administration (30 min infusion)		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Tumor Biopsies															
Newly Obtained Tumor Biopsies [20]	X					X[20]				X[20]					
Archival Tumor Tissues [21]	X														

1 Routine laboratory tests (serum chemistry; hematology) for screening should be performed within 10 days of enrollment.
2 Written consent must be obtained prior to performing any protocol specific procedure. Results of a test performed as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame (e.g. within 28 days prior to Cycle 1, Day 1). Assign Baseline number when the study informed consent is signed.
3 Includes history of treatment for the primary diagnosis, including prior systemic, radiation treatment and surgical treatment, and best response to prior systemic treatments. Date of last prior cancer treatment must be documented. Radiographic studies performed prior to study entry may be collected for review by the investigator. Report complete medication history for 30 days prior to the screening visit (Visit 1).
4 Vital signs to include temperature, pulse, respiratory rate and blood pressure. If a patient's baseline weight does not fluctuate by more than 10%, this weight can be used to calculate dose.
5 Electrocardiogram (12-lead ECG) should be performed at Screening, at the time of PK blood collection for PK (Cmax) within 30 minutes after the end of the first infusion of MK-3475, post dose at Cycle 6, and at the mandatory Safety Follow-up visit.
6 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. Study site should contact the patient mid-cycle (approximately 10 days post-dose) to assess for potential irAEs.

7 See Appendix 6.1 for list of laboratory tests. Routine laboratory tests (e.g., CBC with differential; comprehensive serum chemistry panel; urinalysis) will be performed by the local study site laboratory or their contract laboratory. Following Week 36, urinalysis should be performed every 9 weeks. CBC, serum chemistry and urinalysis may be collected up to 48 hours prior to any Cycle "X", Day 1 dosing.

8 PT/INR and aPTT should be collected at Screening and at the mandatory Safety Follow-up Visit after discontinuation of study therapy. Coagulation parameters should be determined throughout the study when clinically indicated. PT/INR and aPTT will be analyzed by the local study site laboratory.

9 For women of reproductive potential, a urine 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. Women with amenorrhea for <2 years and who have not had a hysterectomy and oophorectomy will only be considered not to be of reproductive potential if they have a documented FSH value in the postmenopausal range.

10 Analysis of T3, FT4 and TSH will be performed by a central laboratory. Following Cycle 2, testing will be performed every other cycle.

11 Analysis of IgG and IgM will be performed by the local study site laboratory. Following Cycle 2, testing will be performed every other cycle.

12 Collected prior to dosing in Cycle 1 and Cycle 2, and then in every other subsequent cycle. Include antinuclear antibodies; anti-DNA antibodies; antithyroglobulin antibodies; antimicrosomal antibodies; and anticardiolipin antibodies. When a blood sample is positive for antinuclear antibodies (i.e., titer of ≥40), it will be tested for antibodies against extractable nuclear antigens. Analysis will be performed by a central laboratory.

13 Blood for anti-MK-3475 antibodies should be collected in Cycles 1, 2, 5, 9 and 13. Subsequently, testing should be performed approximately every 12 weeks for the first 12 months on the study, and approximately every 6 months thereafter. All samples should be drawn within 24 hours before infusion of MK-3475 and at the same time as blood collection for C_{trough}

14 Procedures for collection of samples are described in the Procedures Manual. Peak and trough samples will be collected at Cycles 1 and 2. A trough sample should be collected at Cycle 5. Subsequently, trough samples should be collected approximately every 12 weeks for the first 12 months on the study, then approximately every 6 months thereafter. All trough samples should be drawn within 24 hours before infusion of MK-3475 and at the same time as blood collection for anti-MK-3475 antibodies. The two peak samples in Cycles 1 and 2 should be drawn within 30 minutes after the end of the infusion.

15 Collected before start of infusion. FACS analysis of lymphocyte subpopulations will be performed in a central laboratory.

16 Testing will be performed by the local laboratory at Screening. Include HCV RNA (qualitative), HBsAg, and HIV 1/2 antibodies.

17 Blood collected at predose of Cycle 1 and before infusion of MK-3475 in Cycles 2, 3, 5 and 7. Analysis will be performed by a central laboratory

18 Tumor imaging (either CT or MRI, with strong preference for CT; lung x-ray) will be performed within 30 days prior to enrollment. The same imaging technique has to be used in a patient throughout the study. After first documentation of response or progression, repeat imaging is required approximately 4 weeks later for confirmation, as per immune related response criteria (irRC) guidelines (see Appendix 6.5) (see Section 2.4.1). Tumor imaging will be performed approximately every 12 weeks (or whenever clinically indicated) while the patient remains on study therapy regardless of Cycle/Day. Response status will be assessed by the study site and by a central imaging vendor. The process for collection of CT images and transmission to the central vendor for purpose of central response review is described in the Procedures Manual. Refer to Section 3.3.1.3 of the protocol for additional information. If a tumor biopsy was obtained from a target lesion during eligibility assessment, it is preferred to obtain a new baseline scan.

19 Ipilimumab-refractory patients must send pre-trial scans confirming investigator-determined PD (according to irRC) to the central imaging vendor. Details are provided in the Procedures Manual.

20 A newly obtained biopsy of at least one tumor lesion is mandatory at baseline (prior to Cycle 1/Day 1). A baseline biopsy obtained for other purposes (i.e., not a PN001 study procedure), prior to signing consent, can be utilized if obtained within 60 days of first dose of MK-3475 (Cycle 1 Day 1). Additional biopsy samples approximately at Week 12, Week 24, and at disease progression are highly desirable. When it is feasible, more than one biopsy should be performed at a given time point (e.g., from the same lesion or from different lesions). Further biopsy samples may be obtained at time points other than those specified here if deemed appropriate by the investigator. The tissue sample should have proper size to enable all planned biomarker analyses (e.g., IHC of PD-L1, PD-1, PD-L2; RNA signature profiling), but not artificially decrease the longest diameter of the lesion. Fine needle aspiration will not be acceptable. The biopsy techniques allowed in the study include tru cut core biopsies or surgical biopsies. Study sites should use the same biopsy techniques in this study as they routinely use for a given tumor lesion/location. Biopsy of lesions on study should be limited to non-target lesions or new lesions if their pathologic etiology is ambiguous. Detailed instructions for tissue collection, processing and shipment are provided in the Procedures Manual. If the subject signs the Future Biomedical Research (FBR) consent, any leftover tissue that would ordinarily be discarded at the end of the main study will be retained for FBR, again providing the patient has signed the FBR consent.

21 Collection of archival tumor tissue for purpose of biomarker analysis is strongly encouraged. For patients enrolled with Amendment 07 and 08, collection of archival tumor tissue is mandatory and samples from fine needle aspiration will not be acceptable. An archival specimen is mandatory to be submitted within 3 weeks from the day a patient signs informed consent. Patients who do not have an archival specimen can only be enrolled after discussion with the sponsor. Specific instructions for tissue collection and shipment are provided in the Procedures Manual. If the subject signs the Future Biomedical Research (FBR) consent, any leftover tissue that would ordinarily be discarded at the end of the main study will be retained for FBR, again providing the patient has signed the FBR consent.

22 Required at screening for patients without documented BRAF status. Analysis will be performed by a central laboratory.

23 Informed consent for future biomedical research samples must be obtained before the DNA sample. DNA sample for analysis should be obtained predose, on Day 1 (or with the next scheduled blood draw), as the last sample drawn, on randomized subjects only, or at a later date as soon as the informed consent is obtained. This sample should only be taken once from each subject.

24 Collected in patients enrolled with Amendment 06, 07 and 08..

Part C: 3 Week Schedule

	Screening [1] (-28 to 1 days)	Week/Cycle (21 Days ± 2 Days)													Cycle 14, 15, etc (21 Days ± 2 Days)
Week (approximate)		0	3	6	9	12	15	18	21	24	27	30	33	36	N
Cycle		1	2	3	4	5	6	7	8	9	10	11	12	13	N
Study Procedures															
Informed Consent [2]	X														
Informed Consent for Future Biomedical Research (optional)	X														
Inclusion/Exclusion Criteria	X														
Demographics/Medical History/ Prior Medications [3]	X														
Vital Signs/Weight [4]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECOG Performance Status	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-Lead ECG [5]	X	X													
Review Adverse Events [6]		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Review Concomitant Medications		X	X	X	X	X	X	X	X	X	X	X	X	X	X
CBC with Differential [7]	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Comprehensive Serum Chemistry Panel [7]	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Coagulation Parameters [8]	X														
Urinalysis [7]	X	X			X			X			X			X	X [7]

Part C: 3 Week Schedule (cont)															
	Screening [1] (-28 to 1 days)	Week/Cycle (21 Days ± 2 Days)													Cycle 14, 15, etc (21 Days ± 2 Days)
Week (approximate)		0	3	6	9	12	15	18	21	24	27	30	33	36	N
Cycle		1	2	3	4	5	6	7	8	9	10	11	12	13	N
Study Procedures															
Pregnancy Test - Urine or Serum β-HCG [9]	X														
Thyroid Function [10]		X	X		X		X		X		X		X		X[10]
Immunoglobulins [11]		X	X		X		X		X		X		X		X[11]
Auto-Antibodies [12]		X	X		X		X		X		X		X		X[12]
Anti-MK-3475 Antibodies [13]		X	X			X				X				X	X[13]
Pharmacokinetics [14]		X	X			X				X				X	X[14]
Lymphocyte Subtyping (FACS) [15]		X	X	X	X										
Cytokine/Chemokine Panel [16]		X	X	X	X										
HIV, Hepatitis B and C [17]	X														
Proteomics and RNA Signature Profiling in Blood [18]		X	X	X		X		X							
Blood for Future Biomedical Research[22] (optional)		X													
Efficacy Measurements															
Tumor Imaging [19]	X				X[19]			X[19]			X[19]			X[19]	X[19]

Part C: 3 Week Schedule (cont)

	Screening [1] (-28 to 1 days)	Week/Cycle (21 Days ± 2 Days)													Cycle 14, 15, etc (21 Days ± 2 Days)
Week (approximate)		0	3	6	9	12	15	18	21	24	27	30	33	36	N
Cycle		1	2	3	4	5	6	7	8	9	10	11	12	13	N
Drug Administration															
Study Drug Administration (30 minute infusion)		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Tumor Biopsies															
Archival Tumor Tissues [20]	X														
Newly Obtained Tumor Biopsy[21]	X				X[21]			X[21]							

1 Routine laboratory tests (serum chemistry; hematology) for screening should be performed within 10 days of enrollment.
2 Written consent must be obtained prior to performing any protocol specific procedure. Results of a test performed as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame (e.g. within 28 days prior to Cycle 1, Day 1). Assign Baseline number when the study informed consent is signed.
3 Includes history of treatment for the primary diagnosis, including prior systemic, radiation treatment and surgical treatment, and best response to prior systemic treatments. Date of last prior cancer treatment must be documented. Radiographic studies performed prior to study entry may be collected for review by the investigator. Report complete medication history for 30 days prior to the screening visit (Visit 1).
4 Vital signs to include temperature, pulse, respiratory rate and blood pressure. If a patient's baseline weight does not fluctuate by more than 10%, this weight can be used to calculate dose.
5 Electrocardiogram (12-lead ECG) should be performed at Screening, at the time of PK blood collection for PK (Cmax) within 30 minutes after the end of the first infusion of MK-3475 and at the mandatory Safety Follow-up visit.
6 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. Study site should contact the patient mid-cycle (approximately 10 days post dose) to assess for potential irAEs.

7 See Appendix 6.1 for list of laboratory tests. Routine laboratory tests (e.g., CBC with differential; comprehensive serum chemistry panel; urinalysis) will be performed by the local study site laboratory or their contract laboratory. Following Week 36, urinalysis should be performed every 9 weeks. CBC, serum chemistry and urinalysis may be collected up to 48 hours prior to any Cycle "X", Day 1 dosing.

8 PT/INR and aPTT should be collected at Screening and at the mandatory Safety Follow-up Visit after discontinuation of study therapy. Coagulation parameters should be determined throughout the study when clinically indicated. PT/INR and aPTT will be analyzed by the local study site laboratory.

9 For women of reproductive potential, a urine 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. Women with amenorrhea for <2 years and who have not had a hysterectomy and oophorectomy will only be considered not to be of reproductive potential if they have a documented FSH value in the postmenopausal range.

10 Analysis of T3, FT4 and TSH will be performed by a central laboratory. Following Cycle 2, testing will be performed every other cycle.

11 Analysis of IgG and IgM will be performed by the local study site laboratory. Following Cycle 2, testing will be performed every other cycle.

12 Collected prior to dosing in Cycle 1 and Cycle 2, and then in every other subsequent cycle. Include antinuclear antibodies; anti-DNA antibodies; antithyroglobulin antibodies; antimicrosomal antibodies; and anticardiolipin antibodies. When a blood sample is positive for antinuclear antibodies (i.e., titer of ≥40), it will be tested for antibodies against extractable nuclear antigens. Analysis will be performed by a central laboratory.

13 Blood for anti-MK-3475 antibodies should be collected in Cycles 1, 2, 5, 9 and 13. Subsequently, testing should be performed approximately every 12 weeks for the first 12 months on the study, and approximately every 6 months thereafter. All samples should be drawn within 24 hours before infusion of MK-3475 and at the same time as blood collection for C_{trough}.

14 Procedures for collection of samples are described in the Procedures Manual. Peak and trough samples will be collected at Cycles 1 and 2. A trough sample should be collected at Cycle 5. Subsequently, trough samples should be collected approximately every 12 weeks for the first 12 months on the study, then approximately every 6 months thereafter. All trough samples should be drawn within 24 hours before infusion of MK-3475 and at the same time as blood collection for anti-MK-3475 antibodies. The two peak samples in Cycles 1 and 2 should be drawn within 30 minutes after the end of the infusion.

15 Collected before start of infusion. FACS analysis of lymphocyte subpopulations will be performed in a central laboratory.

16 Collected before start of infusion. Includes multi-analysis panels (MAPs) such as Cytokine MAPAv1.0 and MAPBv1.0, and OncologyMAPv1.0 from RulesBasedMedicine. Analysis of cytokines/chemokines will be performed by a central laboratory.

17 Testing will be performed by the local laboratory at Screening. Include HCV RNA (qualitative), HBsAg, and HIV 1/2 antibodies.
18 Blood collected at predose of Cycle 1 and before infusion of MK-3475 in Cycles 2, 3, 5 and 7. Analysis will be performed by a central laboratory.
19 Tumor imaging (either CT or MRI, with strong preference for CT; lung x-ray) will be performed within 30 days prior to enrollment. The same imaging technique has to be used in a patient throughout the study. After first documentation of response or progression, repeat imaging is required approximately 4 weeks later for confirmation, as per immune related response criteria (irRC) guidelines (see Appendix 6.5) (see Section 2.4.1). Tumor imaging will be performed approximately every 9 weeks (or whenever clinically indicated) while the patient remains on study therapy regardless of Cycle/Day. Response status will be assessed by the study site and by a central imaging vendor. The process for collection of CT images and transmission to the central vendor for purpose of central response review is described in the Procedures Manual. Refer to Section 3.3.1.3 of the protocol for additional information. If a tumor biopsy was obtained from a target lesion during eligibility assessment, it is preferred to obtain a new baseline scan.
20 Collection of archival tumor tissue for purpose of biomarker analysis is strongly encouraged. Specific instructions for tissue collection and shipment are provided in the Procedures Manual. If the subject signs the Future Biomedical Research (FBR) consent, any leftover tissue that would ordinarily be discarded at the end of the main study will be retained for FBR, again providing the patient has signed the FBR consent.
21 A newly obtained biopsy of at least one tumor lesion is mandatory at baseline (prior to Cycle 1/Day 1). A baseline biopsy obtained for other purposes (i.e., not a PN001 study procedure), prior to signing consent, can be utilized if obtained within 60 days of first dose of MK-3475 (Cycle 1 Day 1). Additional biopsy samples approximately at Week 9, Week 18, and at disease progression are highly desirable. When it is feasible, more than one biopsy should be performed at a given time point (e.g., from the same lesion or from different lesions). Further biopsy samples may be obtained at time points other than those specified here if deemed appropriate by the investigator. The tissue sample should have proper size to enable all planned biomarker analyses (e.g., IHC of PD-L1, PD-1, PD-L2; RNA signature profiling). Fine needle aspiration will not be acceptable. The biopsy techniques allowed in the study include tru cut core biopsies or surgical biopsies. Study sites should use the same biopsy techniques in this study as they routinely use for a given tumor lesion/location. Detailed instructions for tissue collection, processing and shipment are provided in the Procedures Manual. If the subject signs the Future Biomedical Research (FBR) consent, any leftover tissue that would ordinarily be discarded at the end of the main study will be retained for FBR, again providing the patient has signed the FBR consent.
22 Informed consent for future biomedical research samples must be obtained before the DNA sample. DNA sample for analysis should be obtained predose, on Day 1 (or with the next scheduled blood draw), as the last sample drawn, on randomized subjects only, or at a later date as soon as the informed consent is obtained. This sample should only be taken once from each subject

Part D: 3 Week Schedule															
	Screening [1] (-28 to 1 days)	Week/Cycle (21 Days ± 2 Days)													Cycle 14, 15, etc (21 Days ± 2 Days)
Week (approximate)		0	3	6	9	12	15	18	21	24	27	30	33	36	N
Cycle		1	2	3	4	5	6	7	8	9	10	11	12	13	N
Study Procedures															
Informed Consent [2]	X														
Informed Consent for Future Biomedical Research (optional)	X														
Inclusion/Exclusion Criteria	X														
Demographics/Medical History/ Prior Medications [3]	X														
Vital Signs/Weight [4]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECOG Performance Status	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-Lead ECG [5]	X	X	X				X								
Review Adverse Events [6]		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Review Concomitant Medications		X	X	X	X	X	X	X	X	X	X	X	X	X	X
CBC with Differential [7]	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Comprehensive Serum Chemistry Panel [7]	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Coagulation Parameters [8]	X														
Urinalysis [7]	X	X			X			X			X			X	X

Part D: 3 Week Schedule (cont)															
	Screening [1] (-28 to 1 days)	Week/Cycle (21 Days ± 2 Days)													Cycle 14, 15, etc (21 Days ± 2 Days)
Week (approximate)		0	3	6	9	12	15	18	21	24	27	30	33	36	N
Cycle		1	2	3	4	5	6	7	8	9	10	11	12	13	N
Study Procedures															
Pregnancy Test - Urine or Serum β-HCG [9]	X														
Thyroid Function [10]		X	X		X		X		X		X		X		X[10]
Immunoglobulins [11]		X	X		X		X		X		X		X		X[11]
Auto-Antibodies [12]		X	X		X		X		X		X		X		X[12]
Anti-MK-3475 Antibodies [13]		X		X			X		X				X		X[13]
Pharmacokinetics [14]		X[21]	X	X			X		X				X		X[14]
Lymphocyte Subtyping (FACS) [15]		X	X	X	X										
HIV, Hepatitis B and C [16]	X														
Proteomics and RNA Signature Profiling in Blood [17]		X	X	X		X		X							
BRAF Testing[22]	X														
Blood for Future Biomedical Research[23](optional)		X													
Efficacy Measurements															
Tumor Imaging [18]	X					X[18]				X[18]				X[18]	X[18]

Part D: 3 Week Schedule (cont)

	Screening [1] (-28 to 1 days)	Week/Cycle (21 Days ± 2 Days)													Cycle 14, 15, etc (21 Days ± 2 Days)
Week (approximate)		0	3	6	9	12	15	18	21	24	27	30	33	36	N
Cycle		1	2	3	4	5	6	7	8	9	10	11	12	13	N
Drug Administration															
Study Drug Administration (30 min infusion)		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Tumor Biopsies															
Newly Obtained Tumor Biopsies [19]	X					X[19]				X[19]					
Archival Tumor Tissues [20]	X														

1 Routine laboratory tests (serum chemistry; hematology) for screening should be performed within 10 days of enrollment.
2 Written consent must be obtained prior to performing any protocol specific procedure. Results of a test performed as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame (e.g. within 28 days prior to Cycle 1, Day 1). Assign Baseline number when the study informed consent is signed.
3 Includes history of treatment for the primary diagnosis, including prior systemic, radiation treatment and surgical treatment, and best response to prior systemic treatments. Date of last prior cancer treatment must be documented. Radiographic studies performed prior to study entry may be collected for review by the investigator. Report complete medication history for 30 days prior to the screening visit (Visit 1).
4 Vital signs to include temperature, pulse, respiratory rate and blood pressure. If a patient's baseline weight does not fluctuate by more than 10%, this weight can be used to calculate dose.
5 Electrocardiogram (12-lead ECG) should be performed at Screening, prior to dosing in Cycle 1, at the time of PK blood collection for PK (Cmax) within 30 minutes after the end of the first infusion of MK-3475, postdose in Cycle 2 and Cycle 6, and at the mandatory Safety Follow-up visit.
6 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. Study site should contact the patient mid-cycle (approximately 10 days post dose) to assess for potential irAEs.

7 See Appendix 6.1 for list of laboratory tests. Routine laboratory tests (e.g., CBC with differential; comprehensive serum chemistry panel; urinalysis) will be performed by the local study site laboratory or their contract laboratory. Following Week 36, urinalysis should be performed every 9 weeks. CBC, serum chemistry and urinalysis may be collected up to 48 hours prior to any Cycle "X", Day 1 dosing.

8 PT/INR and aPTT should be collected at Screening and at the mandatory Safety Follow-up Visit after discontinuation of study therapy. Coagulation parameters should be determined throughout the study when clinically indicated. PT/INR and aPTT will be analyzed by the local study site laboratory.

9 For women of reproductive potential, a urine 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. Women with amenorrhea for <2 years and who have not had a hysterectomy and oophorectomy will only be considered not to be of reproductive potential if they have a documented FSH value in the postmenopausal range.

10 Analysis of T3, FT4 and TSH will be performed by a central laboratory. Following Cycle 2, testing will be performed every other cycle.

11 Analysis of IgG and IgM will be performed by the local study site laboratory. Following Cycle 2, testing will be performed every other cycle.

12 Collected prior to dosing in Cycle 1 and Cycle 2, and then in every other subsequent cycle. Include antinuclear antibodies; anti-DNA antibodies; antithyroglobulin antibodies; antimicrosomal antibodies; and anticardiolipin antibodies. When a blood sample is positive for antinuclear antibodies (i.e., titer of ≥40), it will be tested for antibodies against extractable nuclear antigens. Analysis will be performed by a central laboratory.

13 Blood for anti-MK-3475 antibodies should be collected in Cycles 1, 3, 6, 8 and 12. Subsequently, testing should be performed approximately every 12 weeks for the first 12 months on the study, and approximately every 6 months thereafter. All samples should be drawn within 24 hours before infusion of MK-3475 and at the same time as blood collection for C_{trough}.

14 Procedures for collection of samples are described in the Procedures Manual. Predose/trough MK-3475 PK samples will be collected at Cycles 1, 2, 3, and 6. Peak samples will be collected at Cycles 1 and 6. All predose/trough samples should be drawn within 24 hours before infusion of MK-3475 and at the same time as blood collection for anti-MK-3475 antibodies. The peak samples in Cycles 1 and 6 should be drawn within 30 minutes after the end of the MK-3475 infusion. For Cycle 8 and beyond, C_{trough} only samples will be collected within 24 hours before infusion of MK-3475 and at the same time as blood collection for anti-MK-3475 antibodies. A sample should also be drawn at the visit in which a decision is made to stop study.

15 Collected before start of infusion. FACS analysis of lymphocyte subpopulations will be performed in a central laboratory.

16 Testing will be performed by the local laboratory at Screening. Include HCV RNA (qualitative), HBsAg, and HIV 1/2 antibodies.

17 Blood collected at predose of Cycle 1 and before infusion of MK-3475 in Cycles 2, 3, 5 and 7. Analysis will be performed by a central laboratory.

18 Tumor imaging (either CT or MRI, with strong preference for CT; lung x-ray) will be performed within 30 days prior to enrollment. The same imaging technique has to be used in a patient throughout the study. After first documentation of response or progression, repeat imaging is required approximately 4 weeks later for confirmation, as per immune related response criteria (irRC) guidelines (see Appendix 6.5) (see Section 2.4.1). Tumor imaging will be performed approximately every 9 weeks (or whenever clinically indicated) while the patient remains on study therapy regardless of Cycle/Day. Response status will be assessed by the study site and by a central imaging vendor. The process for collection of CT images and transmission to the central vendor for purpose of central response review is described in the Procedures Manual. Refer to Section 3.3.1.3 of the protocol for additional information. If a tumor biopsy was obtained from a target lesion during eligibility assessment, it is preferred to obtain a new baseline scan.

19 A newly obtained biopsy of at least one tumor lesion is mandatory at baseline (prior to Cycle 1/Day 1). A baseline biopsy obtained for other purposes (i.e., not a PN001 study procedure), prior to signing consent, can be utilized if obtained within 60 days of first dose of MK-3475 (Cycle 1 Day 1). Additional biopsy samples approximately at Week 12, Week 24, and at disease progression are highly desirable. Further biopsy samples may be obtained at time points other than those specified here if deemed appropriate by the investigator. When it is feasible, more than one biopsy should be performed at a given time point (e.g., from the same lesion or from different lesions), but does not artificially decrease the longest diameter of the lesion. The tissue sample should have proper size to enable all planned biomarker analyses (e.g., IHC of PD-L1, PD-1, PD-L2; RNA signature profiling). Fine needle aspiration will not be acceptable. The biopsy techniques allowed in the study include tru cut core biopsies or surgical biopsies. Study sites should use the same biopsy techniques in this study as they routinely use for a given tumor lesion/location. Biopsy of lesions on study should be limited to non-target lesions or new lesions if their pathologic etiology is ambiguous. Detailed instructions for tissue collection, processing and shipment are provided in the Procedures Manual. If the subject signs the Future Biomedical Research (FBR) consent, any leftover tissue that would ordinarily be discarded at the end of the main study will be retained for FBR, again providing the patient has signed the FBR consent.

20 Collection of archival tumor tissue for purpose of biomarker analysis is strongly encouraged. Specific instructions for tissue collection and shipment are provided in the Procedures Manual. If the subject signs the Future Biomedical Research (FBR) consent, any leftover tissue that would ordinarily be discarded at the end of the main study will be retained for FBR, again providing the patient has signed the FBR consent.

21 An additional sample must be drawn between 1 to 3 days (24 to 72 hours) after Cycle 1 Day 1 dosing.

22 Required at screening for patients without documented BRAF status. Analysis will be performed by a central laboratory.

23 Informed consent for future biomedical research samples must be obtained before the DNA sample. DNA sample for analysis should be obtained predose, on Day 1 (or with the next scheduled blood draw), as the last sample drawn, on randomized subjects only, or at a later date as soon as the informed consent is obtained. This sample should only be taken once from each subject.

Part F: 3 Week Schedule

	Screening[1,24] (-42 to 1 days)	Week/Cycle (21 Days ± 2 Days)													Cycle 14, 15, etc (21Days ± 2 Days)
Week (approximate)		0	3	6	9	12	15	18	21	24	27	30	33	36	N
Cycle		1	2	3	4	5	6	7	8	9	10	11	12	13	N
Study Procedures															
Informed Consent [2]	X														
Informed Consent for Future Biomedical Research (optional)	X														
Inclusion/Exclusion Criteria	X														
Demographics/Medical History/ Prior Medications [3]	X														
Vital Signs/Weight [4]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECOG Performance Status	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-Lead ECG [5]	X	X					X								
Review Adverse Events [6]		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Review Concomitant Medications		X	X	X	X	X	X	X	X	X	X	X	X	X	X
CBC with Differential [7]	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Comprehensive Serum Chemistry Panel [7]	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Coagulation Parameters [8]	X														
Urinalysis [7]	X					X				X				X	X [7]

Part F: 3 Week Schedule (cont)															
	Screening[1,24] (-42 to 1 days)	Week/Cycle (21 Days ± 2 Days)													Cycle 14, 15, etc (21Days ± 2 Days)
Week (approximate)		0	3	6	9	12	15	18	21	24	27	30	33	36	N
Cycle		1	2	3	4	5	6	7	8	9	10	11	12	13	N
Study Procedures															
Pregnancy Test - Urine or Serum β-HCG [9]	X														
Thyroid Function [10]		X	X		X		X		X		X		X		X[10]
Immunoglobulins [11]		X	X		X		X		X		X		X		X[11]
Auto-Antibodies [12]		X	X		X		X		X		X		X		X[12]
Anti-MK-3475 Antibodies [13]		X		X			X		X				X		X[13]
Pharmacokinetics [14]		X[21]	X	X			X		X				X		X[14]
Lymphocyte Subtyping (FACS) [15]		X	X	X	X										
HIV, Hepatitis B and C [16]	X														
Proteomics and RNA Signature Profiling in Blood [17]		X	X	X		X		X							
Human leukocyte antigen (HLA)		X													
Blood for Future Biomedical Research[22] (optional)		X													
Pulmonary Function Test[25]	X														
Efficacy Measurements															
Tumor Imaging [18]	X				X[18]			X[18]			X[18]			X[18]	X[18]

Part F: 3 Week Schedule (cont)

	Screening[1,24] (-42 to 1 days)	Week/Cycle (21 Days ± 2 Days)													Cycle 14, 15, etc (21Days ± 2 Days)
Week (approximate)		0	3	6	9	12	15	18	21	24	27	30	33	36	N
Cycle		1	2	3	4	5	6	7	8	9	10	11	12	13	N
Drug Administration															
Administer MK-3475 (30 minute infusion)		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Tumor Biopsies															
Archival Tumor Tissues [19]	X[24]														
Newly Obtained Tumor Biopsy[20]	X[24]				X[20]			X[20]							
EGFR mutation and EML4-ALK translocation[23]	X[24]														

1 Routine laboratory tests (serum chemistry; hematology) for screening should be performed within 10 days of enrollment.
2 Written consent must be obtained prior to performing any protocol specific procedure. Results of a test performed as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame (e.g. within 42 days prior to Cycle 1, Day 1). Assign Baseline number when the study informed consent is signed.
3 Includes history of treatment for the primary diagnosis, including prior systemic, radiation treatment and surgical treatment, and best response to prior systemic treatments. Date of last prior cancer treatment must be documented. Radiographic studies performed prior to study entry may be collected for review by the investigator. Report complete medication history for 30 days prior to the screening visit (Visit 1).
4 Vital signs to include temperature, pulse, respiratory rate and blood pressure. If a patient's baseline weight does not fluctuate by more than 10%, this weight can be used to calculate dose.
5 Electrocardiogram (12-lead ECG) should be performed once at Screening, prior to dosing in Cycle 1, at the time of PK blood collection for PK (Cmax) within 30 minutes after the end of the first infusion of MK-3475. Triplicate 12-lead ECG measurements should be collected at the pre-dose and post dose at Cycle 1 (Cmax), and only post dose of Cycle 6 (Cmax).

6 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. Study site should contact the patient mid-cycle (approximately 10 days post dose) to assess for potential irAEs.
7 See Appendix 6.1 for list of laboratory tests. Routine laboratory tests (e.g., CBC with differential; comprehensive serum chemistry panel; urinalysis) will be performed by the local study site laboratory or their contract laboratory. Following Week 36, urinalysis should be performed every 12 weeks. CBC, serum chemistry and urinalysis may be collected up to 48 hours prior to any Cycle "X", Day 1 dosing.
8 PT/INR and aPTT should be collected at Screening and at the mandatory Safety Follow-up Visit after discontinuation of study therapy. Coagulation parameters should be determined throughout the study when clinically indicated. PT/INR and aPTT will be analyzed by the local study site laboratory.
9 For women of reproductive potential, a urine 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. Women with amenorrhea for <2 years and who have not had a hysterectomy and oophorectomy will only be considered not to be of reproductive potential if they have a documented FSH value in the postmenopausal range.
10 Analysis of T3, FT4 and TSH will be performed by a central laboratory. Following Cycle 2, testing will be performed every other cycle.
11 Analysis of IgG and IgM will be performed by the local study site laboratory. Following Cycle 2, testing will be performed every other cycle.
12 Collected prior to dosing in Cycle 1 and Cycle 2, and then in every other subsequent cycle. Include antinuclear antibodies; anti-DNA antibodies; antithyroglobulin antibodies; antimicrosomal antibodies; and anticardiolipin antibodies. When a blood sample is positive for antinuclear antibodies (i.e., titer of ≥40), it will be tested for antibodies against extractable nuclear antigens. Analysis will be performed by a central laboratory.
13 Blood for anti-MK-3475 antibodies should be collected in Cycles 1, 3, 6, 8, and 12. Subsequently, testing should be performed approximately every 12 weeks for the first 12 months on the study, and approximately every 6 months thereafter. All samples should be drawn within 24 hours before infusion of MK-3475 and at the same time as blood collection for C_{trough}.
14 Procedures for collection of samples are described in the Procedures Manual. Predose/trough MK-3475 PK samples will be collected at Cycles 1, 2, 3, and 6. Peak samples will be collected at Cycles 1 and 6. All predose/trough samples should be drawn within 24 hours before infusion of MK-3475 and at the same time as blood collection for anti-MK-3475 antibodies. The peak samples in Cycles 1 and 6 should be drawn within 30 minutes after the end of the MK-3475 infusion. For Cycle 8 and beyond, C_{trough} only samples will be collected within 24 hours before infusion of MK-3475 and at the same time as blood collection for anti-MK-3475 antibodies. A sample should also be drawn at the visit in which a decision is made to stop study.
15 Collected before start of infusion. FACS analysis of lymphocyte subpopulations will be performed in a central laboratory.
16 Testing will be performed by the local laboratory at Screening. Include HCV RNA (qualitative), HBsAg, and HIV 1/2 antibodies.
17 Blood collected at predose of Cycle 1 and before infusion of MK-3475 in Cycles 2, 3, 5 and 7. Analysis will be performed by a central laboratory.

18 Tumor imaging (either CT or MRI, with strong preference for CT; lung x-ray) will be performed within 30 days prior to enrollment. The same imaging technique has to be used in a patient throughout the study. After first documentation of response or progression, repeat imaging is required approximately 4 weeks later for confirmation, as per immune related response criteria (irRC) guidelines (see Appendix 6.5) (see Section 2.4.1). Tumor imaging will be performed approximately every 9 weeks (or whenever clinically indicated) while the patient remains on study therapy regardless of Cycle/Day. Response status will be assessed by the study site and by a central imaging vendor. The process for collection of CT images and transmission to the central vendor for purpose of central response review is described in the Procedures Manual. Refer to Section 3.3.1.3 of the protocol for additional information. If a tumor biopsy was obtained from a target lesion during eligibility assessment, it is preferred to obtain a new baseline scan.

19 Collection of archival tumor tissue for purpose of biomarker analysis is strongly encouraged. Specific instructions for tissue collection and shipment are provided in the Procedures Manual. If the subject signs the Future Biomedical Research (FBR) consent, any leftover tissue that would ordinarily be discarded at the end of the main study will be retained for FBR, again providing the patient has signed the FBR consent.

20 Newly obtained biopsy is mandatory at baseline (prior to Cycle 1/Day 1). A baseline biopsy obtained for other purposes (i.e., not a PN001 study procedure), prior to signing consent, can be utilized if no other systemic therapy has been administered for the patient's cancer from the time of the biopsy to the first dose of MK-3475 (Cycle 1 Day 1). Additional biopsy samples approximately at Week 9, Week 18, and at disease progression are highly desirable. When it is feasible, more than one biopsy should be performed at a given time point (e.g., from the same lesion or from different lesions). Further biopsy samples may be obtained at time points other than those specified here if deemed appropriate by the investigator. The tissue sample should have proper size to enable all planned biomarker analyses (e.g., IHC of PD-L1, PD-1, PD-L2; RNA signature profiling). Fine needle aspiration will not be acceptable. The biopsy techniques allowed in the study include tru cut core biopsies or surgical biopsies. Study sites should use the same biopsy techniques in this study as they routinely use for a given tumor lesion/location. Detailed instructions for tissue collection, processing and shipment are provided in the Procedures Manual. If the subject signs the Future Biomedical Research (FBR) consent, any leftover tissue that would ordinarily be discarded at the end of the main study will be retained for FBR, again providing the patient has signed the FBR consent.

21 An additional sample must be drawn between 1 to 3 days (24 to 72 hours) after Cycle 1 Day 1 dosing.

22 Informed consent for future biomedical research samples must be obtained before the DNA sample. DNA sample for analysis should be obtained predose, on Day 1 (or with the next scheduled blood draw), as the last sample drawn, on randomized subjects only, or at a later date as soon as the informed consent is obtained. This sample should only be taken once from each subject.

23 Required at Screening for patients without source documentation of results of such testing. If not available at the site, the analysis will be performed by a central laboratory. A newly obtained biopsy or archival biopsy for ALK/EGFR testing is required if the sample is analyzed via the central vendor.

24 Results of tumor tissue analysis to determine of PD-L1 expression, EGFR status, and EML4-ALK status should be obtained prior to initiating other Screening procedures.

25 Collection of FEV1, FVC, pulse oximetry, forced expiratory flow 25-75% (FEF 25-75), PEF, and DLCO.

Part F: 2 Week Schedule

	Screening[1,24] (-42 to 1 days)	Week/Cycle (14 Days ± 2 Days)													Cycle 14, 15, etc (14Days ± 2 Days)
Week (approximate)		0	2	4	6	8	10	12	14	16	18	20	22	24	N
Cycle		1	2	3	4	5	6	7	8	9	10	11	12	13	N
Study Procedures															
Informed Consent [2]	X														
Informed Consent for Future Biomedical Research (optional)	X														
Inclusion/Exclusion Criteria	X														
Demographics/Medical History/ Prior Medications [3]	X														
Vital Signs/Weight [4]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECOG Performance Status	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-Lead ECG [5]	X	X								X					
Review Adverse Events [6]		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Review Concomitant Medications		X	X	X	X	X	X	X	X	X	X	X	X	X	X
CBC with Differential [7]	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Comprehensive Serum Chemistry Panel [7]	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Coagulation Parameters [8]	X														
Urinalysis [7]	X							X						X	X [7]

Part F: 2 Week Schedule (cont)

	Screening[1,24] (-42 to 1 days)	Week/Cycle (14 Days ± 2 Days)														Cycle 14, 15, etc (14Days ± 2 Days)
Week (approximate)		0	2	4	6	8	9	10	12	14	16	18	20	22	24	N
Cycle		1	2	3	4	5	NA	6	7	8	9	10	11	12	13	N
Study Procedures																
Pregnancy Test - Urine or Serum β-HCG [9]	X															
Thyroid Function [10]		X	X		X			X		X		X		X		X[10]
Immunoglobulins [11]		X	X		X			X		X		X		X		X[11]
Auto-Antibodies [12]		X	X		X			X		X		X		X		X[12]
Anti-MK-3475 Antibodies [13]		X		X				X		X				X		X[13]
Pharmacokinetics [14]		X[21]	X	X				X		X				X		X[14]
Lymphocyte Subtyping (FACS) [15]		X	X	X	X											
HIV, Hepatitis B and C [16]	X															
Proteomics and RNA Signature Profiling in Blood [17]		X	X	X		X			X							
Human leukocyte antigen (HLA)		X														
Blood for Future Biomedical Research[22] (optional)		X														
Pulmonary Function Test[25]	X															
Efficacy Measurements																
Tumor Imaging [18]	X						X[18]					X[18]				

Part F: 2 Week Schedule (cont)

	Screening[1,24] (-42 to 1 days)	Week/Cycle (14 Days ± 2 Days)													Cycle 14, 15, etc (14Days ± 2 Days)
Week (approximate)		0	2	4	6	8	10	12	14	16	18	20	22	24	N
Cycle		1	2	3	4	5	6	7	8	9	10	11	12	13	N
Drug Administration															
Administer MK-3475 (30 minute infusion)		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Tumor Biopsies															
Archival Tumor Tissues [19]	X[24]														
Newly Obtained Tumor Biopsy[20]	X[24]					X[20]					X[20]				
EGFR mutation and EML4-ALK translocation[23]	X[24]														

1 Routine laboratory tests (serum chemistry; hematology) for screening should be performed within 10 days of enrollment.
2 Written consent must be obtained prior to performing any protocol specific procedure. Results of a test performed as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame (e.g. within 42 days prior to Cycle 1, Day 1). Assign Baseline number when the study informed consent is signed.
3 Includes history of treatment for the primary diagnosis, including prior systemic, radiation treatment and surgical treatment, and best response to prior systemic treatments. Date of last prior cancer treatment must be documented. Radiographic studies performed prior to study entry may be collected for review by the investigator. Report complete medication history for 30 days prior to the screening visit (Visit 1).
4 Vital signs to include temperature, pulse, respiratory rate and blood pressure. If a patient's baseline weight does not fluctuate by more than 10%, this weight can be used to calculate dose.
5 Electrocardiogram (12-lead ECG) should be performed once at Screening, prior to dosing in Cycle 1, at the time of PK blood collection for PK (Cmax) within 30 minutes after the end of the first infusion of MK-3475. Triplicate 12-lead ECG measurements should be collected at the pre-dose and post dose at Cycle 1 (Cmax), and only post dose of Cycle 9 (Cmax).

6 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. Study site should contact the patient mid-cycle (approximately 10 days post dose) to assess for potential irAEs.

7 See Appendix 6.1 for list of laboratory tests. Routine laboratory tests (e.g., CBC with differential; comprehensive serum chemistry panel; urinalysis) will be performed by the local study site laboratory or their contract laboratory. Following Week 24, urinalysis should be performed every 12 weeks. CBC, serum chemistry and urinalysis may be collected up to 48 hours prior to any Cycle "X", Day 1 dosing.

8 PT/INR and aPTT should be collected at Screening and at the mandatory Safety Follow-up Visit after discontinuation of study therapy. Coagulation parameters should be determined throughout the study when clinically indicated. PT/INR and aPTT will be analyzed by the local study site laboratory.

9 For women of reproductive potential, a urine 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. Women with amenorrhea for <2 years and who have not had a hysterectomy and oophorectomy will only be considered not to be of reproductive potential if they have a documented FSH value in the postmenopausal range.

10 Analysis of T3, FT4 and TSH will be performed by a central laboratory. Following Cycle 2, testing will be performed every other cycle.

11 Analysis of IgG and IgM will be performed by the local study site laboratory. Following Cycle 2, testing will be performed every other cycle.

12 Collected prior to dosing in Cycle 1 and Cycle 2, and then in every other subsequent cycle. Include antinuclear antibodies; anti-DNA antibodies; antithyroglobulin antibodies; antimicrosomal antibodies; and anticardiolipin antibodies. When a blood sample is positive for antinuclear antibodies (i.e., titer of ≥40), it will be tested for antibodies against extractable nuclear antigens. Analysis will be performed by a central laboratory.

13 Blood for anti-MK-3475 antibodies should be collected in Cycles 1, 3, 6, 8, and 12. Subsequently, testing should be performed approximately every 12 weeks for the first 12 months on the study, and approximately every 6 months thereafter. All samples should be drawn within 24 hours before infusion of MK-3475 and at the same time as blood collection for C_{trough}.

14 Procedures for collection of samples are described in the Procedures Manual. Predose/trough MK-3475 PK samples will be collected at Cycles 1, 2, 3, and 6. Peak samples will be collected at Cycles 1 and 6. All predose/trough samples should be drawn within 24 hours before infusion of MK-3475 and at the same time as blood collection for anti-MK-3475 antibodies. The peak samples in Cycles 1 and 6 should be drawn within 30 minutes after the end of the MK-3475 infusion. For Cycle 8 and beyond, C_{trough} only samples will be collected within 24 hours before infusion of MK-3475 and at the same time as blood collection for anti-MK-3475 antibodies. A sample should also be drawn at the visit in which a decision is made to stop study.

15 Collected before start of infusion. FACS analysis of lymphocyte subpopulations will be performed in a central laboratory.

16 Testing will be performed by the local laboratory at Screening. Include HCV RNA (qualitative), HBsAg, and HIV 1/2 antibodies.

17 Blood collected at predose of Cycle 1 and before infusion of MK-3475 in Cycles 2, 3, 5 and 7. Analysis will be performed by a central laboratory.

18 Tumor imaging (either CT or MRI, with strong preference for CT; lung x-ray) will be performed within 30 days prior to enrollment. The same imaging technique has to be used in a patient throughout the study. After first documentation of response or progression, repeat imaging is required approximately 4 weeks later for confirmation, as per immune related response criteria (irRC) guidelines (see Appendix 6.5) (see Section 2.4.1). Tumor imaging will be performed approximately every 9 weeks (or whenever clinically indicated) while the patient remains on study therapy regardless of Cycle/Day. Response status will be assessed by the study site and by a central imaging vendor. The process for collection of CT images and transmission to the central vendor for purpose of central response review is described in the Procedures Manual. Refer to Section 3.3.1.3 of the protocol for additional information. If a tumor biopsy was obtained from a target lesion during eligibility assessment, it is preferred to obtain a new baseline scan.

19 Collection of archival tumor tissue for purpose of biomarker analysis is strongly encouraged. Specific instructions for tissue collection and shipment are provided in the Procedures Manual. If the subject signs the Future Biomedical Research (FBR) consent, any leftover tissue that would ordinarily be discarded at the end of the main study will be retained for FBR, again providing the patient has signed the FBR consent.

20 Newly obtained biopsy of at least one tumor lesion is mandatory at baseline (prior to Cycle 1/Day 1). A baseline biopsy obtained for other purposes (i.e., not a PN001 study procedure), prior to signing consent, can be utilized if no other systemic therapy has been administered for the patient's cancer from the time of the biopsy to the first dose of MK-3475 (Cycle 1 Day 1). Additional biopsy samples approximately at Week 9, Week 18, and at disease progression are highly desirable. When it is feasible, more than one biopsy should be performed at a given time point (e.g., from the same lesion or from different lesions). Further biopsy samples may be obtained at time points other than those specified here if deemed appropriate by the investigator. The tissue sample should have proper size to enable all planned biomarker analyses (e.g., IHC of PD-L1, PD-1, PD-L2; RNA signature profiling), but not artificially decrease the longest diameter of the lesion. Fine needle aspiration will not be acceptable. The biopsy techniques allowed in the study include tru cut core biopsies or surgical biopsies. Study sites should use the same biopsy techniques in this study as they routinely use for a given tumor lesion/location. Biopsy of lesions on study should be limited to non-target lesions or new lesions if their pathological etiology is ambiguous. Detailed instructions for tissue collection, processing and shipment are provided in the Procedures Manual. If the subject signs the Future Biomedical Research (FBR) consent, any leftover tissue that would ordinarily be discarded at the end of the main study will be retained for FBR, again providing the patient has signed the FBR consent.

21 An additional sample must be drawn between 1 to 3 days (24 to 72 hours) after Cycle 1 Day 1 dosing.

22 Informed consent for future biomedical research samples must be obtained before the DNA sample. DNA sample for analysis should be obtained predose, on Day 1 (or with the next scheduled blood draw), as the last sample drawn, on randomized subjects only, or at a later date as soon as the informed consent is obtained. This sample should only be taken once from each subject.

23 Required at Screening for patients without source documentation of results of such testing. If not available at the site, the analysis will be performed by a central laboratory. A newly obtained biopsy or archival biopsy for ALK/EGFR testing is required if the sample is analyzed via the central vendor.

24 Results of tumor tissue analysis to determine of PD-L1 expression, EGFR status, and EML4-ALK status should be obtained prior to initiating other Screening procedures.

25 Collection of FEV1, FVC, pulse oximetry, forced expiratory flow 25-75% (FEF 25-75), PEF, and DLCO.

Part B, C, D, F: Follow-Up				
	Safety Follow-up Visit 30 Days (± 3 days) From Last Dose [1]	Follow-Up (FU) [2]		Long Term Follow-up [11]
Approx Months from Last Dose	*1*	*3*	*6*	*Q 60 days after FU 2*
Visit		FU 1	FU 2[12]	SFU N
Vital Signs/Weight [3]	X	X	X	
12-Lead ECG	X[14]			
Review Adverse Events [13]	X	X	X	
Review Medications	X			
Pharmacokinetics [4]	X	X	X	
Thyroid Function [5]	X			
Immunoglobulins [6]	X			
PT/INR and aPTT	X			
Auto-Antibodies [7]	X			
Anti-MK-3475 Antibodies [8]	X	X	X	
CBC with Differential [9]	X			
Comprehensive Serum Chemistry Panel [9]	X			
Urinalysis [9]	X			
Tumor Imaging [10]	X	X	X	X
Survival				X

1 The mandatory Safety Follow-Up visit should be conducted approximately 30 days after the last dose of study therapy or before the initiation of a new treatment, whichever comes first. Patients with an AE of Grade >1 will be further followed until the resolution of the AE to Grade 0-1 or until beginning of a new therapy for their cancer, whichever occurs first.2 Each Follow-Up Visit (FU) has a visit window of ± 1 week. The first follow-up visit (FU 1) should be scheduled 3 months after the last dose of study therapy. Unless otherwise noted in the flow chart, every effort should be made to collect patient information until (1) 6 months from last dose of MK-3475, or (2) the start of a new cancer therapy, whichever occurs first.
3 Vital signs to include temperature, pulse, respiratory rate and blood pressure.
4 Every effort should be made to collect additional PK samples after the Safety Follow-Up Visit at each 3-month FU visit or until start of a new anti-cancer therapy, whichever occurs first.
5 Analysis of T3, FT4 and TSH will be performed by a central laboratory.
6 Analysis of IgG and IgM will be performed by the local study site laboratory.
7 Include antinuclear antibodies; anti-DNA antibodies; antithyroglobulin antibodies; antimicrosomal antibodies; and anticardiolipin antibodies. When a blood sample is positive for antinuclear antibodies (i.e., titer of ≥40), it will be tested for antibodies against extractable nuclear antigens. Analysis will be performed by a central laboratory.
8 Every effort should be made to collect additional blood samples for anti-MK-3475 antibodies after the Safety Follow-Up Visit for up to 6 months from the last dose of MK-3475 or until start of a new anti-cancer therapy, whichever occurs first. Analysis will be performed by a central laboratory.
9 See Appendix 6.1 for list of laboratory tests.
10 The same imaging technique should be used in a patient as used earlier in the study. In patients who discontinue study therapy early without documented disease progression, every effort should be made to continue monitoring their disease status by radiologic imaging. Monitoring should continue 1) until start of a new anti-cancer treatment, (2) until documented disease progression, or (3) until death, whichever occurs first. Radiographic imaging in the Survival Follow-Up may be performed as clinically indicated or per local standard of care.
11 Each Survival Follow-Up Visit (SFU) has a visit window of ± 1 week, and will be conducted via a phone call. The first survival follow-up should be performed approximately 60 days after the FU 2 visit. Every effort should be made to collect patient information every 60 days thereafter to assess for survival status and start of new antineoplastic therapy if applicable. Survival Follow-Up will continue until the Investigator is notified by the Sponsor to discontinue follow-up.
12 Patients who are complete response (CR) will continue to repeat Follow-Up Visit 2 every 3 months until either the end of the study or disease progression. If the patient experiences disease progression, patients will either enter the survival follow-up or have the option to be retreated with MK-3475 per the investigator's discretion.
13 Collection of all AEs through the 30 day Safety Follow up Visit and SAEs through the 6 month follow up (through visit FU2). Drug-related AEs should be reported at any time.
14 Triplicate measurements for Part B patients who are Q2W and initially consented under Amendment 001-07, and Part F patients

Second Course Phase (All Parts) 2 Week Schedule														
	Week/Cycle (14 Days ± 2 Days)													Cycle 14, 15, etc (14 Days ± 2 Days)
Week (approximate)	0	2	4	6	8	10	12	14	16	18	20	22	24	N
Cycle	1	2	3	4	5	6	7	8	9	10	11	12	13	N
Study Procedures														
Inclusion/Exclusion Criteria[1]														
Vital Signs/Weight [2]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECOG Performance Status	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Review Adverse Events [3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Review Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CBC with Differential [4]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Comprehensive Serum Chemistry Panel [4]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Coagulation Parameters [5]	X													
Urinalysis [4]	X						X						X	X
Pregnancy Test - Urine or Serum β-HCG [6]	X													
Thyroid Function [7]	X	X		X		X		X		X		X		X[7]
Efficacy Measurements														
Tumor Imaging [8]	X				X[8]		X[8]			X[8]			X[8]	X[8]
Drug Administration														
Study Drug Administration (30 min infusion)	X	X	X	X	X	X	X	X	X	X	X	X	X	X

1	Patients who attain a CR and discontinue treatment may restart trial treatment if they meet the criteria specified in Section 3.2.5.4.14.
2	Vital signs to include temperature, pulse, respiratory rate and blood pressure. If a patient's baseline weight does not fluctuate by more than 10%, this weight can be used to calculate dose.
3	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. Study site should contact the patient mid-cycle (approximately 7 days post dose) to assess for potential irAEs.
4	See Appendix 6.1 for list of laboratory tests. Laboratory tests for screening or entry into the Second Course Phase should be performed within 10 days prior to the first dose of treatment. Routine laboratory tests (e.g., CBC with differential; comprehensive serum chemistry panel; urinalysis) will be performed by the local study site laboratory or their contract laboratory. Following Week 24, urinalysis should be performed every 12 weeks. CBC, serum chemistry and urinalysis may be collected up to 48 hours prior to any Cycle "X", Day 1 dosing.
5	PT/INR and aPTT should be collected at Cycle 1 and at the mandatory Safety Follow-up Visit after discontinuation of study therapy. Coagulation parameters should be determined throughout the study when clinically indicated. PT/INR and aPTT will be analyzed by the local study site laboratory.
6	For women of reproductive potential, a urine 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. Women with amenorrhea for <2 years and who have not had a hysterectomy and oophorectomy will only be considered not to be of reproductive potential if they have a documented FSH value in the postmenopausal range.
7	Analysis of T3, FT4 and TSH will be performed by a central laboratory. Following Cycle 2, testing will be performed every other cycle.
8	Tumor imaging (either CT or MRI, with strong preference for CT; lung x-ray) will be performed within 28 days prior to restarting with MK-3475 after relapse from CR. The same imaging technique has to be used in a patient throughout the study. After first documentation of response or progression, repeat imaging is required approximately 4 weeks later for confirmation, as per immune related response criteria (irRC) guidelines (see Appendix 6.5). Response status will be assessed by the study site and by a central imaging vendor. The process for collection of CT images and transmission to the central vendor for purpose of central response review is described in the Procedures Manual. The imaging schedule followed for the initial treatment should be followed in the second course phase, even after Week 24, which is every 12 weeks for patients with melanoma and every 9 weeks for patients with NSCLC.

Second Course Phase (All Parts) 3 Week Schedule

	Week/Cycle (21 Days ± 2 Days)													Cycle 14, 15, etc (21 Days ± 2 Days)
Week (approximate)	0	3	6	9	12	15	18	21	24	27	30	33	36	N
Cycle	1	2	3	4	5	6	7	8	9	10	11	12	13	N
Study Procedures														
Inclusion/Exclusion Criteria[1]														
Vital Signs/Weight [2]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECOG Performance Status	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Review Adverse Events [3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Review Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CBC with Differential [4]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Comprehensive Serum Chemistry Panel [4]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Coagulation Parameters [5]	X													
Urinalysis [4]	X				X				X				X	X
Pregnancy Test - Urine or Serum β-HCG [6]	X													
Thyroid Function [7]	X	X		X		X		X		X		X		X[7]
Efficacy Measurements														
Tumor Imaging [8]	X			X[8]	X[8]		X[8]		X[8]	X[8]			X[8]	X[8]
Drug Administration														
Study Drug Administration (30 min infusion)	X	X	X	X	X	X	X	X	X	X	X	X	X	X

1 Patients who attain a CR and discontinue treatment may restart trial treatment if they meet the criteria specified in Section 3.2.5.4.14.

2	Vital signs to include temperature, pulse, respiratory rate and blood pressure. If a patient's baseline weight does not fluctuate by more than 10%, this weight can be used to calculate dose.
3	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. Study site should contact the patient mid-cycle (approximately 7 days post dose) to assess for potential irAEs.
4	See Appendix 6.1 for list of laboratory tests. Laboratory tests for screening or entry into the Second Course Phase should be performed within 10 days prior to the first dose of treatment. Routine laboratory tests (e.g., CBC with differential; comprehensive serum chemistry panel; urinalysis) will be performed by the local study site laboratory or their contract laboratory. Following Week 36, urinalysis should be performed every 12 weeks. CBC, serum chemistry and urinalysis may be collected up to 48 hours prior to any Cycle "X", Day 1 dosing.
5	PT/INR and aPTT should be collected at Cycle 1 and at the mandatory Safety Follow-up Visit after discontinuation of study therapy. Coagulation parameters should be determined throughout the study when clinically indicated. PT/INR and aPTT will be analyzed by the local study site laboratory.
6	For women of reproductive potential, a urine 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. Women with amenorrhea for <2 years and who have not had a hysterectomy and oophorectomy will only be considered not to be of reproductive potential if they have a documented FSH value in the postmenopausal range.
7	Analysis of T3, FT4 and TSH will be performed by a central laboratory. Following Cycle 2, testing will be performed every other cycle.
8	Tumor imaging (either CT or MRI, with strong preference for CT; lung x-ray) will be performed within 28 days prior to restarting with MK-3475 after relapse from CR. The same imaging technique has to be used in a patient throughout the study. After first documentation of response or progression, repeat imaging is required approximately 4 weeks later for confirmation, as per immune related response criteria (irRC) guidelines (see Appendix 6.5). Response status will be assessed by the study site and by a central imaging vendor. The process for collection of CT images and transmission to the central vendor for purpose of central response review is described in the Procedures Manual. The imaging schedule followed for the initial treatment should be followed in the second course phase, even after Week 36, which is every 12 weeks for patients with melanoma and every 9 weeks for patients with NSCLC.

Second Course Phase: Follow-Up				
	Safety Follow-up Visit 30 Days (± 3) From Last Dose [1]	Follow-Up (FU) [2]		Long Term Follow-up [11]
Approx Months from Last Dose	*1*	*3*	*6*	*Q 60 days after FU 2*
Visit		FU 1	FU 2[12]	SFU N
Vital Signs/Weight [3]	X	X	X	
Review Adverse Events [13]	X	X	X	
Review Medications	X			
Thyroid Function [5]	X			
CBC with Differential [9]	X			
Comprehensive Serum Chemistry Panel [9]	X			
Urinalysis [9]	X			
Tumor Imaging [10]	X	X	X	X
Survival				X

1 The mandatory Safety Follow-Up visit should be conducted approximately 30 days after the last dose of study therapy or before the initiation of a new treatment, whichever comes first. Patients with an AE of Grade >1 will be further followed until the resolution of the AE to Grade 0-1 or until beginning of a new therapy for their cancer, whichever occurs first.
2 Each Follow-Up Visit (FU) has a visit window of ± 1 week. The first follow-up visit (FU 1) should be scheduled 3 months after the last dose of study therapy. Unless otherwise noted in the flow chart, every effort should be made to collect patient information until (1) 6 months from last dose of MK-3475, or (2) the start of a new cancer therapy, whichever occurs first.
3 Vital signs to include temperature, pulse, respiratory rate and blood pressure.
5 Analysis of T3, FT4 and TSH will be performed by a central laboratory.

9 See Appendix 6.1 for list of laboratory tests.
10 The same imaging technique should be used in a patient as used earlier in the study. In patients who discontinue study therapy early without documented disease progression, every effort should be made to continue monitoring their disease status by radiologic imaging. Monitoring should continue 1) until start of a new anti-cancer treatment, (2) until documented disease progression, or (3) until death, whichever occurs first.
11 Each Survival Follow-Up Visit (SFU) has a visit window of ± 1 week, and will be conducted via a phone call. The first survival follow-up should be performed approximately 60 days after the FU 2 visit. Every effort should be made to collect patient information every 60 days thereafter to assess for survival status and start of new antineoplastic therapy if applicable. Survival follow-up should continue until the Investigator is notified by the Sponsor to discontinue follow-up.
12 Patients who are complete response (CR) will continue to repeat Follow-Up Visit 2 every 3 months until either the end of the study or disease progression. If the patient experiences disease progression, patients will either enter the survival follow-up or have the option to be retreated with MK-3475 per the investigator's discretion.
13 Collection of all AEs through the 30 day Safety Follow up Visit and SAEs through the 6 month follow up (through visit FU2). Drug-related AEs should be reported at any time.

2. CORE PROTOCOL

2.1 OBJECTIVES AND HYPOTHESES

2.1.1 Primary Objectives

1) To evaluate and characterize the tolerability and safety profile of single agent MK-3475 in adult patients with unresectable advanced carcinoma (including NSCLC or MEL).

   Hypothesis: Intravenous administration of single agent MK-3475 will have acceptable safety and tolerability.

2) To evaluate anti-tumor activity of MK-3475 in MEL and NSCLC per RECIST 1.1.

   Hypothesis: Single agent MK-3475 will show a clinically meaningful response rate (RR) or disease-control-rate (DCR) per RECIST 1.1 in ipilimumab-naïve MEL patients, a clinically meaningful RR per RECIST 1.1 in MEL patients previously treated with ipilimumab, a clinically meaningful RR per RECISTS 1.1 in MEL patients refractory to ipilimumab, and a clinically meaningful RR per RECIST 1.1 in NSCLC patients that merits further investigation (for details, see Section 3.5, Statistical Analysis Plan).

3) To evaluate the extent of tumor response that correlates with the degree of biomarker positivity in the tumors of ipilimumab naïve patients treated with MK-3475 with the intent that the cut point for the PD-L1 assay will be explored and refined with tumor samples from ipilimumab-naïve MEL.

   Hypothesis: We will be able to define a sub-population of ipilimumab-naïve MEL patients whose tumors express PD-L1. These patients will have a clinically meaningful tumor response compared to ipilimumab naïve MEL patients whose tumors do not express PD-L1.

4) To evaluate anti-tumor activity per RECIST 1.1 of MK-3475 in unselected MEL refractory to ipilimumab patients and MEL patients refractory to ipilimumab with PD-L1 expressing tumors.

   Hypothesis: Single agent MK-3475 will show a clinically meaningful response rate (RR) or disease-control-rate (DCR) per RECIST 1.1 in unselected MEL patients refractory to ipilimumab, however single agent MK-3475 will show a more clinically meaningful response rate (RR) or disease-control-rate (DCR) per RECIST 1.1 in MEL patients refractory to ipilimumab with PD-L1 expressing tumors.

5) To evaluate anti-tumor activity per RECIST 1.1 of MK-3475 in patients with NSCLC with at least one prior systemic therapy whose tumors express a high level of PD-L1.

Hypothesis: Single agent MK-3475 will show a clinically meaningful response rate (RR) per RECIST 1.1 in patients with NSCLC with at least one prior systemic therapy whose tumors express a high level of PD-L1.

2.1.2 Secondary Objectives

1) To evaluate the RR of unselected patients with MEL refractory to ipilimumab and MEL naïve to ipilimumab, patients with MEL refractory to ipilimumab and MEL naïve to ipilimumab whose tumors express PD-L1, and patients with NSCLC with at least one prior systemic therapy whose tumors express a high level of PD-L1, per immune-related response criteria.

2) To characterize the PK profile of single agent MK-3475.

3) To evaluate target engagement and modulation in peripheral blood (PD-1 receptor occupancy and modulation of receptor activity).

4) To investigate the relationship between candidate efficacy biomarkers and anti-tumor activity of MK-3475:

   - To evaluate the correlation between PD-L1 expression levels and anti-tumor activity of MK-3475 in patients with melanoma, excluding ipi-refractory patients as stated in the primary objectives, and separately, non-small cell lung cancer.

   - To investigate other biomarkers (e.g., tumor infiltrating lymphocytes, PD-L2, PD-1; ribonucleic acid (RNA) signature profiles) that may correlate with tumor responses.

   - To evaluate differences in tumor tissue characteristics in biopsies taken during or post-treatment with MK-3475 versus baseline.

5) To evaluate response duration, progression-free-survival and overall survival of MEL patients who are treated with MK-3475.

6) To evaluate response duration, progression-free survival and overall survival of NSCLC patients who are treated with MK-3475.

2.1.3 Tertiary Objectives

1) To examine concordance between archival tumor tissues, formalin-fixed, paraffin-embedded tissue (FFPET) and newly obtained frozen tumor tissue with respect to PD-L1 expression and other candidate efficacy biomarkers.

2.2 PATIENT INCLUSION CRITERIA

1) Patient meets the following corresponding requirements for the part of the study they will enroll into:

   In **Part A** of the study, patients must have a histological or cytological diagnosis of MEL or any type of carcinoma, progressive metastatic disease, or progressive locally advanced disease not amenable to local therapy:

   - Please note: Tumor types of primary interest in Part A include but are not limited to malignant MEL, RCC, hepatocellular carcinoma, non-small cell lung cancer, gastric carcinoma, ovarian carcinoma and colorectal carcinoma.

   - Patients must have failed established standard medical anti-cancer therapies for a given tumor type or have been intolerant to such therapy, or in the opinion of the Investigator have been considered ineligible for a particular form of standard therapy on medical grounds.

   In **Part B** of the study, patients must have a histological or cytological diagnosis of MEL with progressive locally advanced or metastatic disease that is not amenable to definitive local therapy with curative intent.

   Ipilimumab-naïve Patients:

   - Patients naive to ipilimumab may not have received more than 2 prior systemic treatment regimens for treatment of MEL.

   Ipilimumab-treated Patients:

   After the first 13 patients are enrolled, patients who have had ipilimumab may be enrolled, provided the following requirements are met:

   - Full resolution of ipilimumab related adverse effects (including immune-related adverse effects) and no treatment for these adverse events (AEs) for at least 4 weeks prior to the time of enrollment.

   - Minimum of 12 weeks from the first dose of ipilimumab and >6 weeks from the last dose.

   - No history of severe immune related adverse effects from ipilimumab (CTCAE Grade 4; CTCAE Grade 3 requiring treatment >4 weeks).

   - Unequivocal PD following a dose of ipilimumab

Ipilimumab-refractory Patients:

With Amendments 05, 06, 07 and 08, patients who have had ipilimumab may be enrolled, provided the following requirements are met (these patients are considered **ipilimumab-refractory**):

- Received at least two doses of ipilimumab (minimum dose of 3 mg/kg).
- Progressive disease after ipilimumab will be defined according to irRC (Appendix 6.5). The initial evidence of PD is to be confirmed by a second assessment, no less than four weeks from the date of the first documented PD, in the absence of rapid clinical progression (this evaluation is based on investigator assessment; SPONSOR will collect imaging scans for retrospective analysis). Once PD is confirmed, initial date of PD documentation will be considered as the date of disease progression.
- Documented disease progression within 24 weeks of the last dose of ipilimumab. Patients who were re-treated with ipilimumab and patients who were on maintenance ipilimumab will be allowed to enter the trial as long as there is documented PD within 24 weeks of the last treatment date (with ipilimumab).
- Resolution of ipilimumab related AEs (including irAEs) back to Grade 0-1 and ≤10 mg/day prednisone or equivalent dose for irAEs for at least two weeks prior to first dose of study drug.
    - No history of severe irAEs from ipilimumab CTCAE Grade 4 requiring steroid treatment.
    - No history of CTCAE Grade 3 irAEs from ipilimumab requiring steroid treatment (>10 mg/day prednisone or equivalent dose) >12 weeks.
    - Minimum of four weeks (wash out period) from the last dose of ipilimumab.
- Patients with BRAF V600mutant melanoma must have had a prior treatment regimen that includes vemurafenib, dabrafenib, or other approved BRAF and/or MEK inhibitors.
- Patient must have progressive disease after the most recent treatment regimen.

In **Part C** of the study, patients must have a histologically-confirmed or cytologically-confirmed diagnosis of non-small cell lung cancer.

- Patient has experienced progression of locally advanced or metastatic NSCLC after two prior systemic antineoplastic regimens (Adjuvant therapy will count as a regimen if administered within 1 year before the relapse).

- Patient has an estimated life expectancy of at least 12 weeks.

In **Part D** of the study, patients must have a histological or cytological diagnosis of MEL with progressive locally advanced or metastatic disease that is not amenable to definitive local therapy with curative intent.

- Patients must be naive to ipilimumab and may not have received more than 2 prior systemic treatment regimens for treatment of MEL.

In **Part F** of the study, patients must have a histologically-confirmed or cytologically-confirmed diagnosis of non-small cell lung cancer,

- Patients have tumor(s) amenable to biopsy.

- Under amendments 07 and 08, patients in F must have a known EGFR mutation and ALK translocation status.

    - Patients in F-1 must be EGFR wild type and without ALK translocation.

    - Patients in F-2 may have an EGFR sensitizing mutation to EGFR tyrosine kinase inhibitor (TKI) therapy or ALK translocation and participate in this study if they have documented progression of their NSCLC on the appropriate tyrosine kinase inhibitor (only erlotinib, gefitinib, or afatinib, or crizotinib, respectively) and have documented progression of their NSCLC on platinum doublet chemotherapy. There is no preferred order of treatment with TKI or platinum doublet therapy, only that progression has been documented on both treatments. If a patient for F-2 is found to have one molecular alteration (either sensitizing EGFR mutation or ALK translocation), then testing for the other alteration is not required.

- Randomized patients in F-1 and patients in F-2 must have tumors that express PD-L1 as determined by a central vendor. The exception is the 40 patients to be enrolled in F-2 whose tumors do not express PD-L1.

- Patients in F-1 must be naive to systemic treatment for NSCLC and have Stage IV disease (adjuvant therapy may not have been administered within 1 year of the relapse).

- Under amendment 06, patients in F-2 must have experienced progression of locally advanced or metastatic NSCLC after at least two prior systemic

antineoplastic regimens (adjuvant therapy will count as a regimen if administered within 1 year before the relapse).

- Under amendments 07 and 08, patients in F-2 who are PD-L1 positive must have experienced progression of locally advanced or metastatic NSCLC after at least one prior systemic antineoplastic regimen, at least one of which must have been a platinum-containing doublet (adjuvant therapy will count as a regimen if administered within 1 year before the relapse). Patients in F-2 who are PD-L1 negative must have received at least two prior lines of systemic therapy.
- Investigator-determined radiographic progression of NSCLC by RECIST 1.1 on the most recent prior therapy (and on a tyrosine kinase inhibitor if the patient has a sensitizing EGFR mutation or ALK translocation) must be determined. The site's study team must have reviewed pre-trial images that are of diagnostic quality from at least 2 dates to confirm that radiographic progression has occurred per RECIST 1.1 following initiation of the prior therapy. Note, the imaging obtained during screening may be one of the dates reviewed. These pre-MK-3475 images should be submitted to the central imaging vendor for a possible retrospective analysis of this eligibility criterion. The central vendor will not be confirming eligibility prior to randomization.
- Those patients who have received prior thoracic radiation with a dose > 30 Gy must wait at least 26 weeks before the first dose of MK-3475.
- Patients in Part F with a tumor at a critical anatomic location, like abutting the thecal sac or compressing a main-stem bronchus, such that an impending catastrophic event is possible, should have that tumor lesion radiated prior to treatment with MK-3475.
- Patient has an estimated life expectancy of at least 12 weeks.

2) Measurable disease:

- In Part A of the study, patients may have non-measurable disease.
- In Part B, C, D, and F of the study, patients must have measurable disease as defined per irRC (Appendix 6.5):

  i. Tumor mass: Must be accurately measurable in 2 perpendicular diameters, with both its longest diameter and its longest perpendicular must be greater than or equal to 10 mm or 2 times the axial slice thickness. Clinical lesions will only be considered measurable when they are superficial, such as skin or palpable lymph node. For MEL patients who are being screened for enrollment in Part B, after approval of Amendment 07, clinical lesions alone

will not be considered as sufficient for enrollment; there must be measurable disease evident on CT imaging.

ii. Malignant lymph nodes: Must be measurable in 2 perpendicular diameters, with both its longest diameter and its longest perpendicular, must be greater than or equal to 15 mm or 2 times the axial slice thickness.

3) Patient is male or female and ≥18 years of age on day of signing informed consent.

4) Patient must have a performance status of 0 or 1 on the Eastern Cooperative Oncology Group (ECOG) Performance Scale (Appendix 6.2).

5) Patient must have adequate organ function as indicated by the following laboratory values.

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1,500 /mcL
Platelets	≥100,000 / mcL
Hemoglobin	≥9 g/dL or ≥5.6 mmol/L[1]
Renal	
Serum creatinine	≤1.5 X upper limit of normal (ULN)
Hepatic	
Serum total bilirubin	≤ 1.5 X ULN **OR**
	Direct bilirubin ≤ ULN for patients with total bilirubin levels > 1.5 ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 X ULN **OR** ≤ 5 X ULN for patients with liver metastases
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT)	≤1.5 X ULN (Only if not using anticoagulants[2])
Activated Partial Thromboplastin Time (aPTT)	≤1.5 X ULN (Only if not using anticoagulants[2])
1 Criteria must be met without a transfusion within 4 weeks of the blood draw 2 If patient is receiving anticoagulants, then value must be within therapeutic range for the condition the patient is being treated for.	

6) Patient (Parts A, B, C, D and F) has voluntarily agreed to participate by giving written informed consent. For Parts B, C, D and F, patient has agreed to a newly obtained biopsy of tumor (that can be biopsied based on investigator's assessment) and to providing the acquired tissue for biomarker analysis. Tissue obtained for the biopsy must not be previously irradiated. No systemic antineoplastic therapy may be received by the patient between the time of the biopsy and the first administration of MK-3475. An archival specimen is mandatory to submit for Part B patients enrolled with Amendment 07; patients who do not have an available archival specimen can only be enrolled after discussion with the Sponsor.

7) Female patient of childbearing potential has a negative urine or serum pregnancy test. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test

will be required. The serum pregnancy test must be negative for the patient to be eligible.

8) Female patients enrolled in the study, who are not free from menses for >2 years, post hysterectomy/oophorectomy, or surgically sterilized, must be willing to use either 2 adequate barrier methods *or* a barrier method plus a hormonal method of contraception to prevent pregnancy or to abstain from heterosexual activity throughout the study, starting with Visit 1 through 120 days after the last dose of study therapy. Approved contraceptive methods include for example; intra uterine device, diaphragm with spermicide, cervical cap with spermicide, male condoms, or female condom with spermicide. Spermicides alone are not an acceptable method of contraception.

   Male patients must agree to use an adequate method of contraception starting with the first dose of study drug through 120 days after the last dose of study therapy.

9) Subject may also provide consent/assent for Future Biomedical Research. However, the subject may participate in the main trial without participating in Future Biomedical Research.

2.3 PATIENT EXCLUSION CRITERIA

A patient meeting any of the following criteria is not eligible to participate in this study:

1) Patient who has had chemotherapy, radioactive, or biological cancer therapy within 4 weeks prior to the first dose of study therapy, or who has not recovered to CTCAE grade 1 or better from the adverse events due to cancer therapeutics administered more than 4 weeks earlier. Patient who has had erlotinib, gefitinib, afatinib, or crizotinib within 1 week prior to the first dose of study therapy, or who has not recovered to CTCAE Grade 1 or better from the adverse events due to any of these drugs administered more than 1 week earlier.

   - Patient who has had ipilimumab therapy may be enrolled in Part B or Part C of the study (after 13 ipilimumab naïve patients are enrolled in Part B) if the requirements specified in Inclusion Criterion 1) are met.

2) Patient is currently participating or has participated in a study of an investigational agent or using an investigational device within 30 days of administration of MK-3475.

3) Patient is expected to require any other form of antineoplastic therapy while on study (including maintenance therapy with another agent for NSCLC).

4) Patient has a medical condition that requires chronic systemic steroid therapy or requires any other form of immunosuppressive medication. However, patients using physiologic replacement doses of hydrocortisone, or its equivalent, will be considered

eligible for this study: up to 20mg hydrocortisone (or 5mg of prednisone) in the morning and 10 mg hydrocortisone (or 2.5mg of prednisone) in the evening.

5) Patient has risk factors for bowel obstruction or bowel perforation (examples include but not limited to a history of acute diverticulitis, intra-abdominal abscess, abdominal carcinomatosis).

6) Patient has a known history of a hematologic malignancy, malignant primary brain tumor or malignant sarcoma, or of another malignant primary solid tumor, unless the patient has undergone potentially curative therapy with no evidence of that disease for 5 years.

   - Note: The time requirement for no evidence of disease for 5 years does not apply to the tumor for which a patient is enrolled in the study. The time requirement also does not apply to patients who underwent successful definitive resection of basal cell carcinoma of the skin, superficial bladder cancer, squamous cell carcinoma of the skin, in situ cervical cancer, or other in situ cancers.

7) Patient has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Patients with previously treated brain metastases may participate provided they are clinically stable for at least 4 weeks prior to study entry, have no evidence of new or enlarging brain metastases and are off steroids for at least 7 days from first dose of MK-3475.

8) Patient previously had a severe hypersensitivity reaction to treatment with another mAb.

9) Patient has a history of pneumonitis or interstitial lung disease

10) Patient has an active autoimmune disease or a documented history of autoimmune disease or syndrome that requires systemic steroids or immunosuppressive agents. Patients with vitiligo or resolved childhood asthma/atopy would be exception to this rule. Patients that require intermittent use of bronchodilators or local steroid injections would not be excluded from the study. Patients with hypothyroidism that is stable on hormone replacement will not be excluded from the study.

11) Patient had prior treatment targeting PD-1: PD-L1 axis or CTLA (with exception of ipilimumab in study Part B and Part C), or was previously randomized in any MK-3475 trial.

   - Examples of such agents include (but are not limited to): Nivolumab (BMS-936558 MDX-1106 or ONO- 4538); Pidilizumab (CT011); AMP-224; BMS-936559 (MDX 1105); MPDL3280A (RG7446); and MEDI4736.

12) Patient has an active infection requiring therapy.

13) Patient is positive for Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies), active Hepatitis B (HBsAg reactive) or Hepatitis C (HCV RNA (qualitative) is detected); patients with negative Hepatitis C antibody testing may not need RNA testing.

14) Patient has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the patient's participation for the full duration of the study, or is not in the best interest of the patient to participate, in the opinion of the treating Investigator.

15) Patient has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.

16) Patient is, at the time of signing informed consent, a regular user (including "recreational use") of any illicit drugs or had a recent history (within the last year) of substance abuse (including alcohol).

17) Patients with symptomatic ascites or pleural effusion. A patient who is clinically stable following treatment for these conditions (including therapeutic thoraco- or paracentesis) is eligible.

18) Patient is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the study.

2.4 STUDY DESIGN AND DURATION

2.4.1 Summary of Study Design

This is an open-label, Phase I study in patients with locally advanced or metastatic MEL, NSCLC, or carcinoma. The study has 5 parts.

Part A (including Part A-1 and A-2)

Part A dose escalation will use a 3+3 design and will enroll cohorts of 3-6 patients with MEL or any type of carcinoma sequentially at escalating doses of 1, 3 and 10 mg/kg. Dose escalation will continue until identification of a MTD, up to a maximum dose of 10 mg/kg. Following completion of the dose escalation, additional patients will be enrolled in Part A-1 and Part A-2 as described in Section 1.6 to further define the PK and pharmacodynamic characteristics.

Radiological assessment of tumor response status should be performed approximately every 2 months for the first 12 months of treatment and approximately every 3 months thereafter. (If considered more appropriate by the investigator, disease monitoring by radiological imaging can continue at 2-month intervals beyond the first 12 months). The same imaging technique as used at baseline has to be used throughout the study.

Patients will be monitored for safety, anti-MK-3475 antibodies and efficacy throughout the study. If available and consented by participating patients, archived tumor tissue will

be collected. In Part A, newly obtained tumor biopsies may be performed for biomarker analysis in select patients with readily accessible tumor lesions and who consent to the biopsies. Ideally, follow-up biopsy should be taken from the same tumor lesion as the baseline biopsy.

In patients who discontinue study therapy early without documented disease progression, every effort should be made to continue monitoring their disease status by radiologic imaging following the guidelines described in Section 3.2.5.4.13 (Duration of Follow-up).

The primary data used for dose escalation and confirmation will be dose limiting toxicity (DLT) in Cycle 1 (see Section 3.2.5.4.7 for details).

Part B

Part B will only enroll patients with MEL. MK-3475 will be administered at 2 mg/kg and 10 mg/kg. The dosing interval to be used in Part B for patients who consent under protocol amendment 001-02 will be repeated Q2W. These patients will continue Q2W dosing until they discontinue study therapy. For patients consented under protocol amendments 001-03, 001-04, 001-05, 001-06, or following approval of the administrative memo dated 06-Jan-2012, dosing will be Q3W. Patients consented under protocol Amendment 07 will be administered 10 mg/kg at either Q2W or Q3W.

It is expected that Part B will enroll approximately 506 patients, including 76 ipilimumab-naïve patients: approximately 61 patients at 10 mg/kg; and 15 patients at 2 mg/kg. Part B will also include approximately 40 patients who had previously received ipilimumab (at 10 mg/kg), approximately 80 patients who are ipilimumab refractory at 2 mg/kg Q3W and 80 patients who are ipilimumab refractory at 10 mg/kg Q3W. Amendment 07 will enroll approximately 115 additional patients at 10 mg/kg Q2W and another 115 patients at 10 mg/kg Q3W irrespective of their prior ipilimumab status (i.e., ipilimumab naïve or previously treated). The first 13 patients enrolled in Part B will be required to be ipilimumab-naive.

Tumor Assessment in Part B

In general, response criteria and patient management will follow the recently described principles and guidelines for immunotherapies of solid tumors [18]. These irRC take into account the observation that some patients with MEL can have a transient tumor flare/tumor progression in the first few months after start of immunotherapy with subsequent disease response. Although all imaging studies will be reviewed by an independent imaging vendor in a retrospective fashion, all clinical decisions will be based on the interpretation of the investigator at the site treating the patient in real time.

After radiological tumor assessment at screening, the first radiological assessment of tumor response status will be performed at Week 12 (± 1 week), unless there is clinical indication warranting earlier radiologic imaging. The same imaging technique as used at baseline has to be used throughout the study.

If imaging at 12 weeks shows stable disease (SD), treatment will be continued and the next imaging studies will be conducted approximately at Week 24.

If imaging at 12 weeks shows a complete response (CR) or partial response (PR), tumor imaging will be repeated at approximately Week 16 to confirm response, per irRC recommendations. Patients will then return to regular scheduled imaging at approximately Week 24, and every 12 weeks subsequently.

If imaging at 12 weeks shows PD, it is at the discretion of the investigator to keep a patient on study treatment or to stop study treatment until repeat imaging will be repeated approximately 4-6 weeks later, in order to confirm PD. Patients that are deemed clinically unstable are not required to have repeat imaging for confirmation. This decision will be based on clinical judgment of a patient's overall clinical condition, including performance status, clinical symptoms, and laboratory data. The patient must meet the following minimal criteria to continue on study between the first radiological indication of progression and confirmation of progression:

1. Absence of symptoms and signs indicating clinically significant PD (including worsening of laboratory values) indicating disease progression.

2. No decline in ECOG performance status

3. Absence of rapid progression of disease or of progressive tumor at critical anatomical sites (e.g., cord compression) requiring urgent alternative medical intervention.

If repeat imaging shows an objective response or stable disease, treatment with MK-3475 will continue/ resume and the next imaging studies will be conducted approximately at Week 24, and every 12 weeks subsequently. If repeat imaging at Week 16 confirms PD, patients will be discontinued from study therapy.

The same paradigm for confirmatory scans of response (4 weeks after the initial finding) or progression of disease (4-6 weeks after the initial finding) is applicable to subsequent planned scanning intervals (e.g., Week 24, Week 36, etc.).

Patients will be monitored regularly for safety, efficacy and anti-MK-3475 antibodies throughout the study, as per the guidelines in Section 1.7. Newly obtained tumor biopsies for biomarker analysis are mandatory prior to the first dose at baseline. If accessible, archived tumor tissue should be also collected for biomarker analysis. Additional tumor biopsies while on study therapy or after discontinuation of study therapy are highly desirable, for comparison of biomarkers to baseline. Timing of the additional biopsies should follow the guidelines described in Section 1.7. If feasible, follow-up tumor biopsies should be ideally taken from the same lesion as the baseline biopsy. All tumor biopsies require prior written patient consent.

In patients who discontinue study therapy early without documented disease progression, every effort should be made to continue monitoring their disease status by radiologic

imaging following the guidelines described in Section 3.2.5.4.13 (Duration of Follow-up).

Part C

Part C will only enroll patients with NSCLC who have experienced progression after two prior systemic anti-tumor regimens. MK-3475 will be administered at a preliminary RP2D, 10 mg/kg. Dosing in Part C will be repeated every 3 weeks. Study treatment will continue until disease progression, unacceptable toxicity, or the investigator considers it in the best interest of a patient to discontinue study therapy.

Patients will be monitored regularly for safety, efficacy and anti-MK-3475 antibodies throughout the study, as per the guidelines in Section 1.7. Newly obtained tumor biopsies for biomarker analysis are mandatory prior to the first dose at baseline. If accessible, archived tumor tissue should be also collected for biomarker analysis. Tumor biopsies require prior written patient consent.

It is expected that Part C will enroll approximately 35 patients at 10 mg/kg.

Tumor Assessment in Part C

With the exception of imaging timelines (described below), the response criteria and patient management will follow the described principles and guidelines as per Part B.

For patients in Part C, following radiological tumor assessment at screening, the first radiological assessment of tumor response status will be performed at Week 9 (± 1 week), unless there is clinical indication warranting earlier radiologic imaging. The same imaging technique as used at baseline has to be used throughout the study.

If imaging at 9 weeks shows stable disease (SD), treatment will be continued and the next imaging studies will be conducted approximately at Week 18.

If imaging at 9 weeks shows a complete response (CR) or partial response (PR), tumor imaging will be repeated at approximately Week 13 to confirm response, per irRC recommendations. Alternatively, patients may wait until the beginning of Week 18 for repeat imaging. Following Week 18, tumor imaging will be conducted approximately every 9 weeks subsequently.

If imaging at 9 weeks shows PD, it is at the discretion of the investigator to keep a patient on study treatment or to stop study treatment until repeat imaging will be repeated approximately 4-6 weeks later, in order to confirm PD. Patients that are deemed clinically unstable are not required to have repeat imaging for confirmation. This decision will be based on clinical judgment of a patient's overall clinical condition, including performance status, clinical symptoms, and laboratory data. The patient must

meet the following minimal criteria to continue on study between the first radiological indication of progression and confirmation of progression:

1. Absence of symptoms and signs indicating clinically significant PD (including worsening of laboratory values) indicating disease progression.

2. No decline in ECOG performance status

3. Absence of rapid progression of disease or of progressive tumor at critical anatomical sites (e.g., cord compression) requiring urgent alternative medical intervention.

If repeat imaging shows an objective response or stable disease relative to baseline, treatment with MK-3475 will continue/ resume and the next imaging studies will be conducted approximately at Week 18, and every 9 weeks subsequently. If repeat imaging at Week 13 confirms PD, patients will be discontinued from study therapy.

The same paradigm for confirmatory scans of response (4 weeks after the initial findings) or progression of disease (4-6 weeks after the initial finding) is applicable to subsequent planned scanning intervals (e.g., Week 18, Week 27, etc.).

Part D

Part D will only enroll patients with MEL. MK-3475 will be administered at 2 mg/kg and 10 mg/kg. The dosing interval used in Part D will be Q3W. Study treatment will continue until disease progression, unacceptable toxicity, or the investigator considers it in the best interest of a patient to discontinue study therapy.

It is expected that Part D will enroll approximately 88 ipilimumab-naïve patients: approximately 44 patients at 2 mg/kg and 44 patients at 10 mg/kg. Patients will be randomized 1:1 and assigned to a treatment group manually by the Sponsor based on a computer-generated allocation schedule.

Tumor Assessment in Part D

The response criteria and patient management will follow the described principles and guidelines as per Part B.

Part F

Part F will enroll approximately 390 patients with NSCLC. All patients in F-1 and most patients in F-2 must have tumors that express PD-L1 to be eligible for enrollment. In F-1, 88 patients whose tumors express PD-L1 and are naïve to systemic treatment will be randomized 1:1, manually by the Sponsor based on a computer-generated allocation schedule, to 10 mg/kg Q2W (44 patients) and 10 mg/kg Q3W (44 patients) using an allocation schedule generated in-house. Under Amendment 06, 32 patients whose tumors express PD-L1 and have had at least two prior lines of systemic therapy will be treated with MK-3475 at 10 mg/kg Q3W. Under Amendment 07, in F-2, an additional 250 patients with 1 or more prior systemic treatments will be treated, 150 at 10 mg/kg Q3W and 100 at 10 mg/kg Q2W. Patients will be randomized 3:2 and assigned to a treatment group manually by the Sponsor based on a computer-generated allocation schedule. These patients in F-2 may be stratified by either weak or strong PD-L1 expression level. Enrollment of patients with weakly positive tumor expression of PD-L1 will be limited to approximately 50% of the Q2W and Q3W patients cohorts. Furthermore, in F-2, forty patients whose tumors do not express PD-L1 and have received at least two prior lines of systemic therapy will receive 10 mg/kg Q2W. Once a patient is eligible for treatment, the Sponsor will inform the site of the appropriate dose to administer.

Tumor Assessment in Part F:

The response criteria and patient management will follow the described principles and guidelines as per Part C.

2.4.2 Definition of Dose-Limiting Toxicities

All toxicities will be graded using National Cancer Institute (NCI) CTCAE Version 4.0 (Appendix 6.4).

The occurrence of any of the following toxicities during Cycle 1 will be considered a DLT, if judged by the Investigator to be possibly, probably or definitely related to study drug administration:

1. Grade 4 non-hematologic toxicity (not laboratory).

2. Grade 4 hematologic toxicity lasting ≥14 days.

3. Grade 3 non-hematologic toxicity (not laboratory) lasting >3 days despite optimal supportive care.

4. Any Grade 3 non-hematologic laboratory value if:

    - Medical intervention is required to treat the patient, or
    - The abnormality leads to hospitalization, or
    - The abnormality persists for >1 week.

5. Febrile neutropenia Grade 3 or Grade 4:

    - Grade 3 is defined as ANC <1000/mm^3 with a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of ≥38 degrees C (100.4 degrees F) for more than one hour
    - Grade 4 is defined as ANC <1000/mm^3 with a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of ≥38 degrees C (100.4 degrees F) for more than one hour, with life-threatening consequences and urgent intervention indicated.

6. Thrombocytopenia <25,000/mm^3 if associated with:

    - A bleeding event which does not result in hemodynamic instability but requires an elective platelet transfusion, or
    - A life-threatening bleeding event which results in urgent intervention and admission to an Intensive Care Unit

7. Grade 5 toxicity (i.e., death).

Replacement of Patients in DLT Period

Patients who received <90% of the MK-3475 infusion in Cycle 1 (e.g., because the infusion had to be discontinued due to an infusion reaction) and did not experience a DLT will not be taken into account in the assessment of the overall DLT rate for the particular dose level cohort and need to be replaced.

If a patient experiences a DLT in Cycle 1, study therapy may be discontinued following discussion and agreement between the Sponsor and Investigator. An alternative consideration may be dose modification of MK-3475 as described in Section 3.2.5.4.9 with continued therapy.

2.4.3 Treatment Plan

The following table (Table 2-1) displays the distribution of patients, along with the respective dose and dosing interval. Patients enrolled under amendments 07 and beyond are in addition to those enrolled under amendment 06.

Table 2-1

Patient Distribution

	Amendment 001-02	Amendment 001-03/04	Amendment 001-05	Amendment 001-06	Amendment 001-07/08	Total N
Part A Dose Escalation	N=10[1]					28 Solid Tumor
Part A-1	N=6[1]					
Part A-2		N=12 (Q3W)				
Part B (MEL)	**Ipilimumab naïve** at 10 mg/kg (Q2W)[2] N=46	**Ipilimumab naïve** at 10 mg/kg (Q3W) N=15				61
	Ipilimumab treated at 10 mg/kg (Q2W)[2] N=20	**Ipilimumab treated** at 10 mg/kg (Q3W) N=20				40
		Ipilimumab naïve at 2 mg/kg (Q3W) N=15				15
			Ipilimumab refractory at 10 mg/kg (Q3W) N=20	**Ipilimumab refractory** at 10 mg/kg (Q3W) N=60		80
			Ipilimumab refractory at 2 mg/kg (Q3W) N=40	**Ipilimumab refractory** at 2 mg/kg (Q3W) N=40		80
					Ipilimumab naïve, or treated at 10 mg/kg Q2W or Q3W N=230	230

Patient Distribution (cont)

	Amendment 001-02	Amendment 001-03/04	Amendment 001-05	Amendment 001-06	Amendment 001-07/08	Total N
Part C (NSCLC)		10 mg/kg (Q3W) N=35				35
Part D (MEL)			**Ipilimumab naïve** at 2 mg/kg (Q3W) N=44			44
			Ipilimumab naïve at 10 mg/kg (Q3W) N=44			44
Part F-1 (NSCLC)				1L: 2 mg/kg (Q3W) N=44	1L: 10 mg/kg (Q2W) N=44	44[3]
				1L: 10 mg/kg (Q3W) N=44	1L: 10 mg/kg (Q3W) N=44	44[3]
Part F-2 (NSCLC)				3L+: 10 mg/kg (Q3W) N=32		32[3]
					3L+: 10 mg/kg (Q2W) N=40	40[4]
					2L+: 10 mg/kg (Q3W) N=150	150[3]
					2L+: 10 mg/kg (Q2W) N=100	100[3]

1L = First line arm
2L+ = Second line or greater arm
3L+ = Third line or greater arm
1 The dosing interval between Cycle 1 and Cycle 2 is 28 days, Cycle 2 and beyond will be repeated every 14 days
2 Patients in Part B are dosed Q2W. With Amendments 001-03, 001-04, 001-05, 001-06, or following approval of the administrative memo dated 06-Jan-2012, new patients are dosed Q3W
3 Patients' tumors express PD-L1
4 Patients tumors do not express PD-L1

Dose escalation in individual patients will not be permitted in this study, except as indicated for patients enrolled in Part A-2. In addition, for detailed guidelines for dose modifications, see Section 3.2.5.4.9.

The DETAILS portion of this document (Section 3) further outlines the treatment plan for the study, including permitted/prohibited medications and supportive care measures.

2.5 LIST OF EFFICACY/PHARMACOKINETIC/IMMUNOGENICITY MEASUREMENTS

The Study Flow Chart (Section 1.7) provides specific details on collection time points. Details of collection procedures are found in the Procedures Manual for this study.

Part A,B, C, D and F

The following evaluations will be performed throughout the course of the study:

- Tumor response assessments by physical examination and tumor imaging by CT or magnetic resonance imaging (MRI), with strong preference for CT
- Anti-MK-3475 antibodies
- PK measurements (for detailed PK profiling in Part A, and for assessment of C_{trough} and terminal half-life in Part B, C, D, and F)
- ECOG performance status

Part A

The following evaluations will be performed throughout the course of the study:

- Standard serum tumor markers (if applicable)

The following evaluations will be performed throughout the first 12 months of the study and at the Safety Follow-Up Visit:

- Pharmacodynamic measurements: PD-1 receptor occupancy and modulation of PD-1 receptor function
- Analysis of lymphocyte subpopulations

The following evaluations will be performed throughout the first 6 months of the study:

- Chemokine/cytokine measurements in blood
- Proteomics and RNA signature profiling in blood

Part B, C, D, and F

The following evaluations will be performed up to Week 12 (Q2W) and Week 18 (Q3W):

- Proteomics and RNA signature profiling in blood

The following evaluations will be performed up to Week 8 (Q2W) and Week 9 (Q3W):

- Analysis of lymphocyte subpopulations
- Chemokine/cytokine measurements in blood (Part C)

2.6 LIST OF SAFETY MEASUREMENTS

The following safety evaluations will be performed at baseline and throughout the course of the study:

- Vital signs
- Physical examinations
- Medical history
- Evaluation of AEs
- ECOG performance status
- Electrocardiogram (ECG)
- Laboratory tests: complete blood count (CBC), serum chemistry, urinalysis, pregnancy test (at screening and during study when clinically indicated), PT/aPTT (at screening, at the Safety Follow-Up Visit, and during the study when clinically indicated)
- Thyroid function
- Auto-antibodies
- Immunoglobulins (IgG, IgM)

The following will be performed only in Cycle 1 of study Part A and A-1:

- Viral antigen recall reactions

Toxicity will be graded and recorded according to NCI CTCAE, version 4.0 (http://ctep.cancer.gov).

Routine laboratory tests (e.g., CBC with differential; comprehensive serum chemistry panel; PT/INR and aPTT; immunoglobulins; urinalysis; urine and serum β-HCG) will be performed by the local study site laboratory. The other laboratory tests will be performed by a central laboratory. Patient treatment and overall management decisions will be based on local laboratory data. Details regarding the amount of blood drawn for testing to be conducted by a central laboratory are provided in the Procedures Manual.

2.7 STATISTICAL ANALYSIS PLAN SUMMARY

Key elements of the statistical analysis plan are summarized below; details are provided in Section 3.5 of the protocol. In particular, details on predictive biomarker analyses are provided in Section 3.5.5.4, sample size and power calculations are provided in Section 3.5.7, and interim analyses are provided in Section 3.5.9.

2.7.1 Efficacy Analyses

Analysis populations

The primary efficacy analyses will be based on the Full Analysis Set (FAS) population. Patients with measurable disease at baseline, which is defined separately under investigator evaluation and central review, who received at least one dose of study treatment will be included in the FAS population. Analyses of PFS and OS are based on the APaT population that consists of all patients who received at least 1 dose of study treatment.

Efficacy endpoints and analysis methods

RR and DCR as assessed per irRC by investigators will serve as primary efficacy endpoints for the ipilimumab-naïve population treated at 10 mg/kg in Part B enrolled through Amendment 4 for internal decision purposes, and the study in this population is considered positive (i.e., demonstration of proof-of-concept) if the outcome in either endpoint is positive. A 95% confidence interval along with a one-sided p-value for testing the null hypothesis based on the binomial distribution will be provided for each for the two primary endpoints: overall RR and overall DCR.

The primary endpoint is RR to demonstrate the anti-tumor activity of MK-3475 in all study populations. The primary measure for assessment of tumor response is based on RECIST 1.1 by blinded central reviewers and the secondary measure is based on irRC by investigators. DCR, response duration and PFS based on both irRC and RECIST 1.1, and OS will serve as secondary endpoints. A 95% confidence interval for RR will be provided for each population and by dose/schedule as applicable. Although DCR is not the primary endpoint, similar analyses will also be provided. In addition, Kaplan-Meier plots and descriptive statistics of progression-free-survival (PFS) and overall survival (OS) will be provided. Further, in order to adjust for short follow-up, Kaplan-Meier plot and descriptive statistics of time-to-response will be provided whereas the Kaplan-Meier estimate of cumulative response rate at the longest follow-up time-point will serve as an estimate of the overall response rate. Response rate based on patients with at least 28 weeks of follow-up will also be provided as an approximate of the overall response rate. Descriptive statistics will also be provided for analysis of response duration and tumor volumetric change. Between-treatment comparisons will be conducted for all efficacy endpoints as appropriate to investigate the dose/schedule difference.

2.7.2 Safety Analyses

The All Patients as Treated (APaT) population will be used for the analysis of safety data in this study. The APaT population consists of all patients who received at least 1 dose of study treatment.

In order for a patient to be considered evaluable for the analysis of DLT, the patient must have either had a DLT in Cycle 1 or had received at least 90% of the prescribed dose of MK-3475 in Cycle 1 and completed all safety evaluations up to and including at least 28 days after the first administration of MK-3475 without experiencing a DLT. A patient without a DLT will replaced if he/she did not adequately complete the evaluation period associated with the first cycle of study therapy (i.e., discontinue prematurely due to a reason unrelated to study therapy) or if that patient received <90% of the prescribed dose.

3. PROTOCOL DETAILS

3.1 BACKGROUND/RATIONALE

Redacted

Redacted

Redacted

Redacted

Redacted

Redacted

Redacted

3.2 STUDY PROCEDURES

3.2.1 Concomitant Medication(s)/Treatment(s)

All treatments that the Investigator considers necessary for a patient'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 study period, documentation of drug dosage, frequency, route, and date will also be included on the CRF.

All concomitant medications received within 30 days before the first dose of study mediation and 30 days after the last infusion of study medication should be recorded.

3.2.2 Prohibited Medications

Patients may receive other medications that the Investigator deems to be medically necessary, with the specific exception of non-protocol specified chemotherapy, radiotherapy, immunotherapy, anti-neoplastic biological therapy or investigational agents other than MK-3475. Patients who in the assessment by the investigator require the use of any of the aforementioned treatments for clinical management should be removed from the study.

Patients are prohibited from receiving live vaccines within 30 days prior to the first dose of study therapy and while participating in study. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, seasonal flu, H1N1 flu, rabies, BCG, and typhoid vaccine.

Section 2.3 of the protocol (Exclusion Criteria) describes other medications which are prohibited in this study. Chemotherapy, radioactive, or biological cancer therapy will not be permitted.

3.2.3 Diet/Activity

Patients should maintain a normal diet.

3.2.4 Pregnancy/Contraception/Nursing

3.2.4.1 Pregnancy Testing

All women who are being considered for participation in the study, and who are not surgically sterilized or postmenopausal, will be tested for pregnancy within 72 hours of receiving the first infusion of study medication. If a urine test is positive or borderline (unable to confirm as negative), a β-hCG test will be required. Patients must be excluded in the event of a positive or borderline test result. The results of the pregnancy test will not be recorded.

3.2.4.2 Contraception

MK-3475 may have adverse effects on a fetus *in utero*. Furthermore, it is not known if MK-3475 has transient adverse effects on the composition of sperm. Non-pregnant, non-breast-feeding women may be enrolled if they are considered highly unlikely to conceive. Highly unlikely to conceive is defined as 1) surgically sterilized, or 2) postmenopausal (a woman who is ≥45 years of age and has not had menses for greater than 2 years will be considered postmenopausal), or 3) amenorrheaic for <2 years without a hysterectomy and oophorectomy and with a documented FSH value in the postmenopausal range, or 4) not heterosexually active for the duration of the study, or 5) heterosexually active and willing to use 2 methods of birth control (which is also recommended for the female partners of male patients). The 2 birth control methods can be 2 barrier methods *or* a barrier method plus a hormonal method to prevent pregnancy, used throughout the study starting with Visit 1 through 120 days after the last dose of study medication. Male patients enrolled in this study must also agree to use an adequate method of contraception starting with Visit 1 through 120 days after the last dose of study drug.

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

Patients should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study they must adhere to the contraception requirement (described above) for the duration of the study. If there is any question that a patient will not reliably comply with the requirements for contraception, that patient should not be entered into the study.

3.2.4.3 Use in Pregnancy

MK-3475 may have adverse effects on a fetus; therefore, women with a positive pregnancy test at screening will not be eligible for enrollment. If a patient inadvertently becomes pregnant while on treatment with MK-3475, the patient will immediately be removed from the study. The site will contact the patient at least monthly and document the patient'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). If a male patient's partner becomes pregnant on study the pregnancy must be reported to the SPONSOR. The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the SPONSOR.

3.2.4.4 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, patients who are breast-feeding are not eligible for enrollment.

3.2.5 Procedures

3.2.5.1 Informed Consent

Study personnel must obtain documented consent from each potential patient prior to entering in a clinical study. Consent must be documented by obtaining the dated signature both of the patient and of the person conducting the consent discussion on the consent form. If local law does not allow written consent, then oral consent, attested to by the dated signature of an impartial witness (someone not involved with the conduct of the study), is the required alternative.

If the patient is illiterate, an impartial witness should be present during the entire informed consent reading and discussion. Afterward, the patient should sign and date the informed consent, if capable. The impartial witness should also sign and date the informed consent along with the individual who read and discussed the informed consent (i.e. study staff personnel).

If the patient is legally incompetent (i.e. a minor or mentally incapacitated), the written consent of a parent, legal guardian or legal representative must be obtained. Depending on local law or review committee requirements such consent may also need to be signed by an impartial witness.

The information from the consent form should be translated and communicated to the patient in language understandable to the patient. When the study patient population includes non-English speaking people, an accurately translated consent form should be provided with a written statement by the translator (whether the translator is the investigator, the Clinical Monitor, or a professional translator), indicating that the consent form is an accurate translation of the accompanying English version.

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

Patients may undergo study screening tests prior to giving written informed consent provided that these tests are considered part of standard care.

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

3.2.5.1.1 Consent and Collection of Specimens for Future Biomedical Research

The investigator or qualified designee will explain the Future Biomedical Research consent to the subject, answer all of his/her questions, and obtain written informed consent before performing any procedure related to the Future Biomedical Research sub-trial. A copy of the informed consent will be given to the subject.

3.2.5.1.2 Future Biomedical Research

The following specimens are to be obtained as part of Future Biomedical Research:

- Blood for genomics use
- Leftover Tumor Biopsy Tissue from the main study.

3.2.5.1.3 HLA Testing

Blood samples will be collected and HLA typing may be performed to determine if anti-tumor immune responses correlate to an individual's HLA alleles.

3.2.5.2 Assignment of Baseline Number/Screening

After the patient has signed the consent form, the site will assign a unique screening (baseline) number. Once assigned, a baseline number cannot be reused for any reason.

After the patient has completed all baseline (screening) procedures and met all requirements of inclusion/exclusion criteria, the treating center will contact the SPONSOR to enroll the patient and provide the required eligibility information (refer to Sections 2.2 and 2.3). The center will complete a Patient Registration Form (refer to Procedure Manual) and fax or email it to the SPONSOR prior to enrolling the patient.

3.2.5.3 Registration/Allocation

Patients who meet the inclusion/exclusion criteria are eligible to enter into the study.

The SPONSOR will assign an Allocation Number (AN) to the patient and return (fax) this information to the center. The AN is a unique number; once assigned, it becomes the permanent study identifier for that patient when they receive their first infusion of MK-3475. In the event a patient is enrolled on the study but does not begin treatment, that patient's allocation number will not be reassigned. Patients who do not meet entry criteria will not be assigned an allocation number.

The center must account for all patients screened and enrolled. A patient participation log is to be completed with the patient's baseline number, allocation number (if patient is enrolled), date of consent, and date of the initial administration of study drug. If a patient is not enrolled, the reason for exclusion from the study will be documented on this log.

Treatment will begin within 7 days from the date of registration (i.e., approval of patient enrollment by SPONSOR and subsequent assignment of an allocation number).

A note referring to inclusion in the study will be documented in the patient medical records along with the allocation number and date of consent. The SPONSOR or SPONSOR's representative will keep the investigators informed of the screening activities, enrollment, and dose group availability.

Patients enrolled in one dose group cannot be re-enrolled in another dose group.

All patients will be given information identifying them as a participant in a research protocol. The information will identify appropriate contact and corresponding telephone number to be utilized in the event of an emergency.

A single patient/subject cannot be assigned more than 1 allocation number.

3.2.5.4 Treatment/Evaluation/Follow-Up

3.2.5.4.1 Study Visits

Procedures should be performed as close to the scheduled time as possible. The exact time at which a procedure is performed must be recorded in the patients study records or appropriate worksheet (if applicable). Any nonscheduled procedures required for urgent evaluation of safety concerns take precedence over all routine scheduled procedures.

A detailed outline of all scheduled study procedures is provided in the Study Flow Charts (Section 1.7). Procedures should be performed at the study center where the patient is being treated.

Blood collections for safety evaluation assume priority over other procedures. Whenever possible, blood samples should be obtained by fresh peripheral venipuncture. If a patient does not have peripheral access, the sample may be collected from a central catheter immediately after an initial withdrawal of at least 10 mL of blood; or preferably, after a series of other blood sample collections from the central catheter.

PK blood sampling will assume priority after blood sampling for safety evaluation. The exact days and times at which PK sampling are performed must be recorded on the CRF.

The patient will be assessed for adverse experiences per the Study Flow Chart (Section 1.7) and at all unscheduled visits.

3.2.5.4.2 Vital Signs

To the extent feasible, blood pressure will be taken on the same arm throughout the study. A large cuff should be used for obese patients. Patients must be resting in a sitting position for 10 minutes prior to obtaining vital signs.

3.2.5.4.2.1 Pulmonary Function

Pulmonary function tests should include an assessment of forced vital capacity, forced expiratory flow between 25 and 75 percent of FVC (FEF25-75), forced expiratory volume in one second and peak expiratory flow (PEF) and diffusion

capacity. Additionally, oxygen saturation as assessed by pulse oximetry is required. These tests should be performed at baseline and subsequently at the discretion of the investigator. Hemoglobin must be obtained within 3 days of pulmonary function testing.

3.2.5.4.3 Medical History

The investigator will obtain the patient's medical history at the Screening visit. 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.

3.2.5.4.4 Physical Examination

A complete physical examination will be performed at the Screening visit. A physical examination with directed evaluation as judged appropriate by the Investigator will be performed as per the flow chart.

3.2.5.4.5 Electrocardiogram (ECG)

In Part A, a 12-lead ECG should be performed at Screening, at the Safety Follow-up Visit, and during study at the time points described in Section 1.7 (Study Flow Chart). Under amendment 07, in Part B, a 12-lead ECG should be performed at Screening, Cycle 1, Cycle 6, and at the Safety Follow-up Visit. Those patients who initially consent under Amendment 07 and are dosed at Q2W in Part B will have a 12-lead ECG performed at Screening, Cycle 1, Cycle 9, and at the Safety Follow-up Visit. These EKGs for the 10 mg/kg Q2W schedule will be in triplicate, except for screening. Those patients who initially consent under Amendment 07 and are dosed at 10 mg/kg Q3W will have a singlet 12-lead ECG performed at screening, Cycle 1, Cycle 6, and at the Safety Follow up Visit. In Part C, a 12-lead ECG should be performed at Screening, Cycle 1, and at the Safety Follow-up Visit. Under Amendment 07, in Part D, a 12-lead ECG should be performed at Screening, Cycle 1, Cycle 2, Cycle 6, and at the Safety Follow-up Visit. In Part F Q3W dosing, a 12-lead ECG should be performed once at Screening, and in triplicate at Cycle 1, Cycle 6, and at the Safety Follow-up Visit. In Part F Q2W dosing, a 12-lead ECG should be performed once at Screening and in triplicate at Cycle 1, Cycle 9, and at the Safety Follow-Up Visit. Please refer to the Study Flow Chart for additional information. EKGs performed during a Cycle will be within 30 minutes after completing administration of MK-3475.

When enough patients treated at 10 mg/kg Q2W from Parts B and F and Q3W from Part F have been enrolled that will permit exclusion that the upper bound of the 90% confidence interval for mean change in QTc from baseline to maximum steady state plasma concentration of MK-3475 is above 20 milliseconds, an analysis will be performed for each schedule. Based on the primary data from this study, the standard deviation of change in QTc from baseline is estimated to be 19.5 milliseconds. With 10/16/34 patients, the study has 90% power to meet the criterion if the true change from baseline is 0/5/10 milliseconds. The half-width of the 90% confidence interval for mean change is 7.2/5.9 milliseconds when the sample size is 20/30. When data from these analyses demonstrate that MK-3475 has a low likelihood of increasing the QTc interval, the rigorous collection of ECG data in triplicate at many time-points will discontinue and

routine monitoring with singlet ECG readings may resume. Sites will be notified via Administrative Memo of this change.

3.2.5.4.6 Guidelines for Study Drug Administration

MK-3475 will be administered as a 30-minute IV infusion, with a window of -5 and +10 minutes (except as indicated in Part A-2).

Part A consists of a dose escalation followed by additional analysis of PK and pharmacodynamic characteristics. Part A will begin with a dose escalation where 3 dose levels of MK-3475 will be evaluated: 1 mg/kg, 3 mg/kg and 10 mg/kg. To ascertain proper PK sampling and analysis, the interval between the first and second dose in Part A will be 28 days. In subsequent cycles, the dosing interval will be 14 days. Part A-1 and A-2 will enroll additional patients to explore the PK and pharmacodynamic characteristics as described in Sections 1.5 and 1.6. Patients in Part A-2 receiving less than 1.0 mg/kg of MK-3475 will have study drug administered via IV push.

Specific instructions for dose calculation, reconstitution, preparation of the infusion fluid, and administration of MK-3475 as both an IV push and infusion are provided in the Procedures Manual.

Patients in Part B will receive MK-3475 at the preliminary RP2D(s) determined in Part A. The dosing interval to be used in Part B for patients who consent under protocol amendment 001-02 will be repeated Q2W. These patients will continue Q2W dosing until they discontinue study therapy. For patients consented under protocol amendments 001-03, 001-04, 001-05, 001-06 or following approval of the administrative memo dated 06-Jan-2012, dosing will be Q3W. Patients who consent under protocol Amendment 07 will receive 10 mg/kg MK-3475 with a dosing interval of either Q2W or Q3W.

Patients in Part C will receive MK-3475 at a preliminary RP2D, 10 mg/kg. The dosing interval will be every 3 weeks.

Patients in Part D will receive MK-3475 at 2 mg/kg and 10 mg/kg. The dosing interval will be every 3 weeks.

Patients in Part F-1 will receive MK-3475 at 10 mg/kg with a dosing interval of Q2W or Q3W. Patients in F-2 under Amendment 06 will receive 10 mg/kg with a dosing interval of Q3W, while F-2 patients enrolled under Amendment 07 will receive 10 mg/kg MK-3475 at dosing intervals of either Q2W or Q3W.

Study treatment will continue until disease progression or unacceptable toxicity or tolerability.

The specific time of study drug 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.

3.2.5.4.7 Rules for Dose Escalation and Continuation

Rules for Part A Dose Escalation

DLTs observed in Cycle 1 will be used to determine escalation to the next dose level. The study is using a traditional 3+3 design and the dose escalation rules are as follows:

- An initial cohort of 3 patients is enrolled.
- If 0/3 patients develops a DLT, escalation to the next dose will occur.
- If 1/3 patients develops a DLT:
    - Another 3 patients will be enrolled at this dose level.
        - If 0 of the 3 new patients develops a DLT (for a total of 1/6 patients with a DLT at this dose level), escalation to the next dose level will occur.
        - If ≥1 of the 3 new patients develops a DLT (for a total of ≥2/6 patients with a DLT at this dose level), the dose escalation stage of the trial will be terminated, and the dose directly below the current dose will be considered the MTD.
- If ≥2/3 patients develop a DLT, the dose escalation stage of the trial will be terminated, and the dose directly below the current dose will be considered the MTD.

It is conceptually acceptable to de-escalate to an intermediate, not pre-defined and not previously-studied dose, if evaluation of toxicity at such a dose is desired. If this approach is taken, 3 new patients should be enrolled at the new intermediate dose, and the aforementioned rules should be used to determine further enrollment at this dose level.

The highest dose to be tested during dose escalation is 10 mg/kg. If 0/3 patients or ≤1/6 patients develop a DLT at that dose, then 10 mg/kg is considered the MTD.

3.2.5.4.8 Preliminary RP2D for Use in Parts B, C, D and F

The doses to be used in Part B of the study will be determined based on the data from Part A. The parameters considered for selection of the preliminary RP2D(s) will include safety profile, PK, pharmacodynamics, and anti-tumor efficacy. Additional patients (approximately 18) will be enrolled in Part A since more robust PK characterization of MK-3475 is deemed warranted as described in Sections 3.1.2 and 3.1.3. Enrollment of these patients and the subsequent dosing is described in Section 1.6.

The dose to be used in Part C will be 10 mg/kg. The doses to be used in Parts D will be 2 mg/kg, and 10 mg/kg and 10 mg/kg in Part F. Amendment 07 will also explore optimal dosing interval in Part B and Part F cohorts.

3.2.5.4.9 Guidelines for Dose Modifications

The following guidelines for dose modification apply to all Parts of the study.

MK-3475 will be withheld for the following adverse reactions:

- A drug-related non-hematological toxicity ≥Grade 2, with the exception of the adverse reactions listed under requirement of permanent discontinuation of study therapy
    - Grade 2 fatigue alone does not require the withholding of study therapy
- A drug-related hematological toxicity Grade 4

In addition, MK-3475 will be withheld for any of the following adverse events. Permanent discontinuation should be considered following discussion with the SPONSOR if any of the following Adverse Events Warranting Potential Dose Modification are experienced:

- Severe or life-threatening adverse reactions, including any of the following:
    - Grade 4 toxicity (non-hematologic or hematologic)
    - Diarrhea with abdominal pain, fever, ileus, or peritoneal signs; increase in stool frequency (7 or more over baseline), stool incontinence, need for intravenous hydration for more than 24 hours, gastrointestinal hemorrhage, and gastrointestinal perforation
    - Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >5 times upper limit of normal
        - For patients with liver metastasis who entered the study with Grade 2 elevation of AST/ALT, MK-3475 will be permanently discontinued if AST/ALT increase ≥ 50% relative to baseline and lasting ≥1 week)
    - Total serum bilirubin >3 times upper limit of normal
    - Steven-Johnson syndrome, toxic epidermal necrolysis, or rash complicated by full thickness dermal ulceration or necrotic, bullous or hemorrhagic manifestations
    - Severe (i.e., CTCAE Grade 3 or 4) motor or sensory neuropathy, Guillain-Barré syndrome, or myasthenia gravis
    - Severe immune-related adverse events involving any other organs (e.g., nephritis, pneumonitis, pancreatitis, non-infectious myocarditis)
    - Immune-mediated ocular disease that is unresponsive to topical immunosuppressive therapy

- Grade 4 infusion reaction

- Grade 2 **clinical immune related** adverse reactions which persist without improvement for >4 weeks

- Inability to reduce corticosteroid dose for immune-related adverse events to ≤10 mg prednisone or equivalent per day

In case a drug related toxicity does not resolve to Grade 0-1 within 12 weeks after last administration of study drug, study therapy discontinuation is recommended. With Investigator and Sponsor agreement, patients with a laboratory adverse event still at Grade 2 may continue in the study only if asymptomatic and controlled.

In patients who continue on study therapy after experiencing an Adverse Event Warranting Potential Dose Modification, if considered drug-related by the investigator, once the patient has recovered to Grade 0-1 the dosing interval in subsequent cycles will be increased by 1 week (e.g., to 3 weeks in patients who were on an every 2-week schedule). Following each such dose delay due to toxicity, the dosing interval should increase by an additional week. For example, patients who began the study on a 3-week dosing schedule, and have stopped drug twice for due to a drug-related toxicity that meets the above criteria, should now be dosing every 5 weeks.

For patients who experience a recurrence of the same severe AEs listed above with rechallenge of MK-3475, a consultation between the Sponsor and Investigator will occur to determine whether the patient should continue in the study. A patient who experiences the same SAE of the same NCI toxicity grade or higher with rechallenge of MK-3475 must discontinue MK-3475 immediately.

Guidelines for Infusion Reactions

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

- CTCAE Grade 1 or 2 infusion reaction: Reduce the infusion rate by 50% for the entire remaining duration of that infusion. Proper medical management should be instituted, as indicated per type of the reaction. This includes but is not limited to an antihistamine (e.g., diphenhydramine or equivalent), anti-pyretic (e.g., paracetamol or

equivalent), and if considered indicated oral or IV glucocorticoids, epinephrine, brochodilators, and oxygen.

  - In the next cycle, the infusion time should be extended to 1 hour. Patients should receive oral premedication with an antihistamine (e.g., diphenhydramine or equivalent) and an anti-pyretic (e.g., paracetamol or equivalent), and they should be closely monitored for clinical signs and symptoms of an infusion reaction.

- CTCAE Grade 3 or 4 infusion reaction: Immediately stop the infusion. Proper medical management should be instituted immediately, as indicated per type and severity of the reaction. This includes but is not limited to oral or IV anti-histamine, anti-pyretic, glucocorticoids, epinephrine, brochodilators, and oxygen.

  - In the event of a Grade 3 or 4 infusion reaction, patients should be discontinued from further study therapy.

3.2.5.4.10 Supportive Care Guidelines

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

- **Diarrhea**: Patients should be monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus). In symptomatic patients, infectious etiologies should be ruled out, and if symptoms are persistent and/or sever, endoscopic evaluation should be considered.
  - In patients with severe enterocolitis, MK-3475 will be held and treatment with systemic corticosteroids should be initiated at a dose of 1 to 2 mg/kg/day of prednisone or equivalent. When symptoms improve to Grade 1 or less, corticosteroid taper should be started and continued over at least 1 month.
  - In patients with moderate enterocolitis, MK-3475 should be withheld and anti-diarrheal treatment should be started. If symptoms are persistent for more than one week, systemic corticosteroids should be initiated (e.g., 0.5 mg/kg/day of prednisone or equivalent). When symptoms improve to Grade 1 or less, corticosteroid taper should be started and continued over at least 1 month. Regarding guidelines for continuing treatment with MK-3475, see Section 3.2.5.4.9.
- All patients who experience diarrhea should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
- **Nausea/vomiting**: Nausea and vomiting should be treated aggressively, and consideration should be given in subsequent cycles to the administration of prophylactic antiemetic therapy according to standard institutional practice. Patients should be strongly encouraged to maintain liberal oral fluid intake.

- **Anemia**: Transfusions and/or erythropoietin may be utilized as clinically indicated for the treatment of anemia, but should be clearly noted as concurrent medications.
- **Neutropenia**: Prophylactic use of colony-stimulating factors including Granulocyte Colony-Stimulating Factor (G-CSF), pegylated G-CSF or Granulocyte Macrophage Colony-Stimulating Factor GM-CSF is not allowed in this study. Therapeutic use of G-CSF is allowed in patients with Grade 3-4 febrile neutropenia.
- **Thrombocytopenia**: Transfusion of platelets may be used if clinically indicated. ITP should be ruled out before initiation of platelet transfusion.
- **Anti-infectives**: Patients with a documented infectious complication should receive oral or IV antibiotics or other anti-infective agents as considered appropriate by the treating Investigator for a given infectious condition, according to standard institutional practice.

3.2.5.4.10.1 Pneumonitis

The treatment of symptomatic patients differs from asymptomatic patients. Patients with symptomatic pneumonitis should immediately stop receiving MK-3475 and have an evaluation, which may include bronchoscopy and pulmonary function tests, to rule out other causes such as infection. If the patient is diagnosed with study drug-associated pneumonitis, the following treatment plan is recommended and should be applied.

Recommended treatment for symptomatic pneumonitis:

- Dose interruption of MK-3475 and steroid intervention for ≤Grade 2 with option to return to treatment if improves to Grade ≤1.
    - Patients should begin a regimen of steroids and taper, if necessary. MK-3475 may be resumed once clinical improvement is observed.
- Immediate and permanent discontinuation if ≥Grade 3.

After improvement to ≤Grade 1 of the pneumonitis the following rules should apply:

- First episode of pneumonitis
    - Improvement occurs in ≤2 weeks – dose MK-3475 at usual schedule of Q2W or Q3W.
    - Improvement occurs in >2 weeks – add an additional week in between MK-3475 dosing (e.g., Q3W now becomes Q4W).
- Second episode of pneumonitis
    - Permanently discontinue MK-3475 if upon rechallenge patient develops pneumonitis ≥Grade 2.

If there is no improvement in the signs of pneumonitis additional diagnostic procedures should be considered, such as bronchoscopy, to confirm the diagnosis.

3.2.5.4.10.2 Adverse Events of Clinical Interest: Immune Related Adverse Events

An immune related adverse event (irAE) may be defined as an adverse event of unknown etiology, associated with drug exposure and is consistent with an immune phenomenon. Efforts should be made to rule out neoplastic, infectious, metabolic, toxin or other etiologic causes prior to labeling an adverse event of clinical interest. Immunological, serological and histological (biopsy) data should be used to support the diagnosis of an immune-related toxicity. If an irAE is noted, appropriate work-up (including biopsy if possible) should be performed. Some immune related adverse events (irAEs) are considered Events of Clinical Interest (ECIs).

In the event a patient develops any of the following irAEs, a detailed narrative of the event should be reported as an ECI to the SPONSOR within 24 hours of the event:

- Grade ≥3 diarrhea
- Grade ≥2 colitis
- Grade ≥2 pneumonitis
- Grade ≥3 hypo- or hyperthyroidism

A separate guidance document has been provided entitled “MK-3475 Event of Clinical Interest and Immune-Related Adverse Event Guidance Document”. This document can be found in the administrative binder and provides guidance regarding identification, evaluation and management of irAEs. Additional AEs that are considered ECIs by the SPONSOR are identified in this guidance document and also need to be reported to the SPONSOR within 24 hours of the event. Depending on the type and severity of the irAE, oral or intravenous treatment with a corticosteroid should be considered, in addition to appropriate symptomatic treatment of a given condition.

Patients should be assessed for possible irAE prior to each dose. Lab results should be evaluated and patients should be asked for signs and symptoms suggestive of an event. Patients who develop irAE should have additional testing to rule out other etiologic causes. If lab results or symptoms indicated a possible irAE then additional testing should be performed to rule out other etiologic causes. If no other cause was found, then it is assumed to be an irAE.

Additional ECIs are described in Section 3.4.8.

3.2.5.4.11 Duration of Therapy

Treatment with MK-3475 may continue until one of the following events occurs:

- Documented disease progression
- Intercurrent illness that prevents further administration of treatment

- Unacceptable adverse experiences (see Section 3.2.5.4.9)
- Patient withdraws consent
- If in the opinion of the Investigator, a change or discontinuation of therapy would be in the best interest of the patient
- Patient is lost to follow-up
- Pregnancy in patient
- Patients who have a confirmed complete response by two scans ≥4 weeks apart and who have been on MK-3475 treatment for at least 6 months may discontinue MK-3475 treatment at the discretion of the investigator after receiving at least two doses beyond the initial determination of CR. See Section 1.6.

If a patient discontinues from the study, the procedures will be followed as described in Section 3.2.5.4.12 and 3.2.5.4.13.

3.2.5.4.12 Safety Follow-up Visit

After a patient is discontinued from study therapy (in Parts A, B, C, D, and F), a mandatory Safety Follow-Up Visit should be performed approximately 30 days after the last infusion of study medication. Procedures and assessments performed at the Safety Follow-Up Visit and beyond should follow the respective guidelines described in the Study Flow Chart (Section 1.7) for Parts A, B, C, D, and F as appropriate.

The patient will be monitored for adverse events up to the mandatory Safety Follow-Up Visit or to resolution of toxicity to Grade 0-1, whichever occurs later. In patients who start another cancer therapy before 30 days after discontinuation of study therapy, the Safety Follow-Up Visit should occur prior to the patient receiving another cancer therapy.

Patients who are eligible for retreatment with MK-3475 (as described in Section 3.2.5.4.14) may have up to two safety follow-up visits, one after the Treatment Period and one after the Second Course Phase.

3.2.5.4.13 Duration of Follow-up

All patients have to be followed for at least 30 days after their last dose of study drug or until initiation of a new anti-cancer treatment, whichever occurs first.

Patients who are discontinued from the study due to an unacceptable drug related adverse event will be followed until the resolution of the AE to Grade 0-1 or stabilization or until beginning of a new therapy for their cancer, whichever occurs first.

In all patients in Part A, every effort should be made to collect blood samples for PK every 4-8 weeks and antibodies to MK-3475 approximately every 2 months after last drug administration, for a total period of 24 weeks. In Parts B, C, and D every effort should be made to collect blood samples for PK and antibodies to MK-3475

approximately every 12 weeks, for a total period of 24 weeks after last drug administration. The first collection of blood samples can be performed at the time of the mandatory Safety Follow-Up Visit.

In Part A patients who discontinued study therapy without documented disease progression, every effort should be made to continue monitoring their disease status by radiologic imaging following the guidelines described in the Study Flow Chart (Section 1.7, Part A). Disease monitoring should continue (1) for approximately 6 months without disease progression, (2) until start of a new anti-cancer treatment, (3) until documented disease progression, or (4) until death, whichever occurs first.

In Parts B, C, D and F, patients who discontinued study therapy without documented disease progression, monitoring of their disease status by radiologic imaging should continue following the guidelines described in the Study Flow Chart (Section 1.7; Parts B, C, D and F: Follow-Up). Disease monitoring should continue (1) until start of a new anti-cancer treatment (information of the new cancer therapy will be collected), (2) until documented disease progression, or (3) until death, whichever occurs first.

For patients in Parts A, B, C, D and F who achieve a CR and who stop study treatment, the mandatory Safety Follow-Up Visit should be performed approximately 30 days after the last infusion of study medication. Procedures and assessments performed at the Safety Follow-Up Visit should follow the respective guidelines described in the Study Flow Chart as appropriate. Beyond the Safety Follow-Up Visit, patients will continue to be monitored for adverse events and followed per the standard follow-up period as described in the Study Flow Chart (Section 1.7). However, CR patients will not exit the standard follow-up, and will continue to return to the clinic every 3 months for the duration of the study following the Follow-Up flow chart. Subjects who are eligible to receive retreatment with MK-3475 according to the criteria in Section 3.2.5.4.14 will move from the follow-up phase to the Second Course Phase when they experience disease progression.

Patients will be followed long-term for survival, as described in the Study Flow Chart (Section 1.7; Parts B, C, D and F: Follow-Up).

3.2.5.4.14 Second Course Phase (Retreatment Period for Post-Complete Remission Relapse ONLY)

Patients may be eligible to receive MK-3475 in the Second Course Phase of this study if the study remains open and the patient meets the following conditions:

- Stopped initial treatment with MK-3475 after attaining an investigator-determined confirmed CR according to irRC
- Was treated for at least 24 weeks with MK-3475 before discontinuing therapy
- Received at least two treatments with MK-3475 beyond the date when the initial CR was declared

- Experienced an investigator-determined progression after stopping their initial treatment with MK-3475
- 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 2.2
- Female patient of childbearing potential should have a negative urine or serum pregnancy test within 72 hours prior to receiving retreatment with study medication.
- Female patients of childbearing potential should be willing to use 2 methods of birth control or be surgically sterile, or a barrier method plus a hormonal method of contraception to prevent pregnancy, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study medication (Reference Section 2.2). Patients of child bearing potential are those who have not been surgically sterilized or have been free from menses for > 2 years (see Section 2.2).
- Male patients 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 patient's participation for the full duration of the trial or is not in the best interest of the patient to participate, in the opinion of the treating investigator.

Patients who restart treatment will be retreated at the dose and dose frequency they received upon initial treatment with MK-3475.

3.2.5.5 Interim Data Locks

Part A

An interim data clean and lock will occur when Part A patient accrual is complete and all patients have completed Cycle 1. The purpose of this interim lock is preliminary analysis of safety, PK and PD, and determination of MTD and preliminary RP2D.

Part B

In addition to the two planned interim analyses (see Section 3.5.8), an interim data clean and lock will occur when Part B patient accrual is complete and all patients have (1) discontinued the study, or (2) been lost to follow up, or (3) been on study treatment for at least 6 months from the start of study therapy, whichever occurs first. The purpose of this interim lock is analysis of safety and efficacy data for administrative program decisions and for external reporting, respectively.

At the time of interim locks in Part A and B, patients may continue study therapy as per protocol guidelines. Study procedures will continue to be followed as per protocol.

Additional interim analyses for Part C, D and F are described in Section 3.5.

3.2.5.6 Discontinuation/Withdrawal from Study

Subjects/patients may withdraw at any time or be dropped from the study at the discretion of the investigator should any untoward effects occur. In addition, a subject/patient may be withdrawn by the investigator or the SPONSOR if he/she violates the study plan or for administrative and/or other safety reasons. The investigator or study coordinator must notify the SPONSOR immediately when a subject/patient has been discontinued/ withdrawn due to an adverse experience (telephone or FAX). When a subject/patient discontinues/withdraws prior to study completion, all applicable activities scheduled for the final study visit should be performed at the time of discontinuation. Any adverse experiences which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 3.4 SAFETY MEASUREMENTS - DETAILS.

Subjects/patients who discontinue from the study for reasons unrelated to the study (e.g., personal reasons) will be replaced as required for the study to meet its objectives. The decision to remove a subject/patient and to replace dropouts will be made jointly by the investigator, SPONSOR Clinical Monitor, and SPONSOR study statistician. The replacement will generally receive the same treatment or treatment sequence (as appropriate) as the allocation number replaced. Both the replacement and originally allocated number will be unique numbers.

3.2.5.7 Withdrawal from Future Biomedical Research

Subjects may withdraw their consent for Future Biomedical Research and have their specimens and all derivatives destroyed. Subjects may withdraw consent at any time by writing to the principal investigator for the main trial. If medical records for the main trial are still available, the Investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@merck.com), and a form will be provided by the Sponsor to obtain appropriate information to complete specimen withdrawal. Subsequently, the subject's specimens will be removed from the biorepository and be destroyed. A letter will be sent from the Sponsor to the investigator confirming the destruction. It is the responsibility of the Investigator to inform the subject of completion of destruction. Any analyses in progress at the time of request for destruction or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research trial data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main trial are no longer available (e.g., if the investigator is no longer required by regulatory agencies to retain the main trial records) or the specimens have been completely anonymized, there will no longer be a link

between the subject's personal information and their specimens. In this situation, the request for specimen destruction cannot be processed.

3.3 EFFICACY / PHARMACOKINETIC / IMMUNOGENICITY, ETC. MEASUREMENTS

3.3.1 Efficacy Measurements

All baseline efficacy evaluations should be performed as close as possible to the beginning of treatment. Baseline imaging must be performed no more than 30 days before enrollment. The same imaging method should be used to characterize each identified and reported lesion at baseline and during follow-up.

Tumor status will be compared to baseline and response will be evaluated by physical examination, anatomic imaging measurement, serum tumor markers (where appropriate), and performance status.

3.3.1.1 Response Criteria

For Parts A, B, C, D and F, tumor response will be determined by investigator assessment with retrospective independent central review.

In Part A, RECIST 1.1 (Appendix 6.3) will be applied for assessment of tumor response. The specific criteria are described in the Investigator's Imaging Operations Manual (IIOM). In addition, evaluation of volumetric tumor response will be performed by a central imaging vendor (see IIOM for details).

In Part B, the irRC (investigator assessment) will be applied as a measure for assessment of tumor response and as basis for all protocol guidelines related to disease status (e.g., discontinuation of study therapy). The irRC system is specifically described in the IIOM and in Appendix 6.5. RECIST 1.1 will also be applied as a measure for assessment of tumor response. In addition, evaluation of volumetric tumor response will be performed by a central imaging vendor (see IIOM for details).

In Part C, the irRC (investigator assessment) will also be applied as a measure for assessment of tumor response and as basis for all protocol guidelines related to disease status (e.g., discontinuation of study therapy). The irRC system is specifically described in the IIOM and in Appendix 6.5. RECIST 1.1 will also be applied as a measure for assessment of tumor response. In addition, evaluation of volumetric tumor response will be performed by a central imaging vendor (see IIOM for details).

In Part D, the irRC (investigator assessed) will be applied as a measure for assessment of tumor response and as basis for all protocol guidelines related to disease status (e.g., discontinuation of study therapy). The irRC system is specifically described in the IIOM and in Appendix 6.5. RECIST 1.1 will also be applied as a measure for assessment of tumor response. In addition, evaluation of volumetric tumor response will be performed by a central imaging vendor (see IIOM for details).

In Part F, the irRC (investigator assessment) will also be applied as a measure for assessment of tumor response and as basis for all protocol guidelines related to disease status (e.g., discontinuation of study therapy). The irRC system is specifically described in the IIOM and in Appendix 6.5. RECIST 1.1 will also be applied as a measure for assessment of tumor response. In addition, evaluation of volumetric tumor response will be performed by a central imaging vendor (see IIOM for details).

The irRC is a recently published set of guidelines proposed for immunotherapies in solid tumors [18]. The guidelines were prompted mostly by the clinical observation that some patients can have a temporary increase in existing tumor lesions or the transient occurrence of a new lesion after start of immunotherapy, while ultimately experiencing treatment benefit in form of an objective disease response or long lasting disease stabilization. Analysis of more than 200 patients with MEL who had received study therapy with ipilimumab showed approximately 10% of patients falling into that category. This subgroup of patients had an overall survival that was comparable to that in patients who had a CR, PR or SD on the basis of traditional WHO criteria [18].

3.3.1.2 Efficacy Endpoints

Part A

In Part A, overall response rate will be used to estimate anti-tumor activity. If applicable, response duration will be determined. Response duration will be measured from first documentation of response to first documentation of disease progression. No other efficacy endpoints will be analyzed in Part A.

Part B

RR and DCR will serve as primary efficacy endpoints for the ipilimumab-naïve population treated at 10 mg/kg in Part B enrolled through Amendment 4 for internal decision making, and the study in this population is considered positive (i.e., demonstration of proof-of-concept in this population) if the outcome in either endpoint is positive. The primary endpoint is RR based on RECIST 1.1 by independent central review to further demonstrate the anti-tumor activity of MK-3475 in all populations and dose/schedules in Part B. DCR, response duration, PFS and OS will serve as secondary endpoints.

Part C

In Part C, the primary endpoint is RR based on RECIST 1.1 by independent central review. DCR, response duration, PFS and OS will serve as secondary endpoints.

Part D

In Part D, the primary endpoint is RR based on RECIST 1.1 by independent central review. DCR, response duration, PFS and OS will serve as secondary endpoints.

Part F

In Part F, the primary endpoint is RR based on RECIST 1.1 by independent central review. DCR, response duration, PFS and OS will serve as secondary endpoints.

3.3.1.3 Radiographic Assessment

In all patients (Parts A, B, C, D and F), baseline tumor imaging (CT or MRI, with a preference for CT) examinations must be performed within 30 days before enrollment. The same imaging technique as used at baseline has to be used throughout the study.

Part A

Part A patients who are on study therapy will have tumor imaging performed approximately every 2 months in the first 12 months and approximately every 3 months thereafter (see also Part A Study Flow Chart [Section 1.7], and Section 3.2.5.4.13).

After first documentation of CR or PR, imaging performed at the next regularly scheduled time point will be used for response confirmation.

Patients who discontinue study therapy without documented disease progression will have tumor imaging performed approximately every 3 months until (1) 6 months without disease progression, (2) start of a new anti-cancer treatment, (3) documented disease progression, or (4) death, whichever occurs first.

Part B

Part B patients will have their first radiological disease assessment on study at Week 12 (± 1 week) unless there is clinical indication warranting earlier imaging.

If disease assessment at Week 12 shows SD, the next imaging will be performed at approximately Week 24.

If disease assessment at Week 12 shows a CR or PR, imaging will be repeated at Week 16 to confirm response, per irRC recommendations. Subsequent imaging will be performed at Week 24.

If imaging at 12 weeks shows PD, it is at the discretion of the investigator to keep a patient on study treatment or to stop study treatment until repeat imaging will be repeated approximately 4-6 weeks later, in order to confirm PD. Patients that are deemed clinically unstable are not required to have repeat imaging for confirmation. This decision will be based on clinical judgment of a patient's overall clinical condition, including performance status, clinical symptoms, and laboratory data. Section 2.4.1 lists the criteria for determining clinical stability. If repeat imaging shows an objective response or stable disease, treatment with MK-3475 will continue/ resume and the next imaging studies will be conducted approximately at Week 24, and every 12 weeks subsequently. If repeat imaging at Week 16 confirms PD, patients will be discontinued from study therapy.

The same paradigm for confirmatory scans of response (4 weeks after the initial finding) or progression of disease (4-6 weeks after the initial finding) is applicable to subsequent planned scanning intervals (e.g., Week 24, Week 36, etc.). After Week 24, imaging will be repeated every 12 weeks +/- 1 week.

Part B patients who discontinue study therapy without documented disease progression will have tumor imaging performed approximately every 3 months until (1) 6 months without disease progression, (2) start of a new anti-cancer treatment, (3) documented disease progression, or (4) death, whichever occurs first.

Part C

With the exception of imaging timelines (described below), the response criteria and patient management will follow the described principles and guidelines as per Part B.

For patients in Part C, following radiological tumor assessment at screening, the first radiological assessment of tumor response status will be performed at Week 9 (± 1 week), unless there is clinical indication warranting earlier radiologic imaging.

If imaging at 9 weeks shows stable disease (SD), treatment will be continued and the next imaging studies will be conducted approximately at Week 18.

If imaging at 9 weeks shows a CR or PR, tumor imaging will be repeated at approximately Week 13 to confirm response, per irRC recommendations. Alternatively, patients may wait until the beginning of Week 18 for repeat imaging. Following Week 18, tumor imaging will be conducted approximately every 9 weeks subsequently.

If imaging at 9 weeks shows PD, it is at the discretion of the investigator to keep a patient on study treatment or to stop study treatment until repeat imaging will be repeated approximately 4-6 weeks later, in order to confirm PD. Patients that are deemed clinically unstable are not required to have repeat imaging for confirmation. This decision will be based on clinical judgment of a patient's overall clinical condition, including performance status, clinical symptoms, and laboratory data. Section 2.4.1 lists the criteria for determining clinical stability. If repeat imaging shows an objective response or stable disease relative to baseline, treatment with MK-3475 will continue/ resume and the next imaging studies will be conducted approximately at Week 18, and every 9 weeks subsequently. If repeat imaging at Week 13 confirms PD, patients will be discontinued from study therapy.

The same paradigm for confirmatory scans of response (4 weeks after the initial findings) or progression of disease (4-6 weeks after the initial finding) is applicable to subsequent planned scanning intervals (e.g., Week 18, Week 27, etc.).

Part D

In Part D, the response criteria and patient management will follow the described principles and guidelines as per Part B.

Part F

The response criteria and patient management will follow the described principles and guidelines as per Part C.

3.3.2 Pharmacokinetic Measurements

Details on collection of blood samples, processing, storage and shipping will be provided in the Procedures Manual.

Part A

PK analysis in Part A will include but is not limited to $AUC_{0\text{-}28day}$, C_{max} and T_{max}, C_{trough} $t_{½}$, Cl and V_d.

The time points for PK blood sampling are described in Section 1.7 (Study Flow Charts: Details of Sampling for Pharmacokinetics and Pharmacodynamics for Part A and A-1 and Details of Sampling for Pharmacokinetics and Pharmacodynamics for Part A-2).

Part B

In Part B, PK profile of MK-3475 will be further characterized using a population modeling approach.

The time points for PK blood sampling are described in Section 1.7 (Part B Study Flow Charts for 2 weeks and 3 weeks).

Part C

In Part C, PK profile of MK-3475 will also be further characterized using a population modeling approach.

The time points for PK blood sampling are described in Section 1.7 (Part C Study Flow Chart).

Part D

In Part D, PK profile of MK-3475 will be further characterized using a population modeling approach.

The time points for PK blood sampling are described in Section 1.7 (Part D Study Flow Charts for 2 weeks and 3 weeks).

Part F

In Part F, PK profile of MK-3475 will also be further characterized using a population modeling approach.

The time points for PK blood sampling are described in Section 1.7 (Part F Study Flow Chart).

3.3.3 Pharmacodynamic Measurements

Pharmacodynamic measurements will only be performed in Part A of the study. Details on collection of blood samples, processing, storage, and shipping details are provided in the Procedures Manual. The time points for pharmacodynamic blood sampling are described in Section 1.7 (Study Flow Charts: Details of Sampling for Pharmacokinetics and Pharmacodynamics for Parts A and A-1, and Details of Sampling for Pharmacokinetics and Pharmacodynamics for Part A-2).

PD-1 receptor occupancy on circulating T-cells will be measured as an indication of target engagement. In addition, an ex-vivo assay will measure induction of IL-2 (a measure of T-cell activity) to assess functional modulation of target activity on circulating T-cells by MK-3475.

3.3.4 Biomarkers

The primary biomarker objective is to assess the relationship between PD-L1 expression levels and anti-tumor activity of MK 3475 in patients with MEL and NSCLC.

The study of single dose nivolumab published data from nine patients who had tissue biopsies from their tumors that were tested for expression of PD-L1 by immunohistochemistry. Three of four patients who demonstrated membranous staining for PD-L1 had regression of their tumor burden. The fourth patient that demonstrated membranous staining for PD-L1 had been treated at the lowest tested dose in the protocol (0.3 mg/kg) and did not experience regression of tumor burden. The remaining five patients who provided tumor tissue for testing did not express PD-L1 and did not experience any clinical response. The authors of this paper believed that a potentially significant correlation between membranous PD-L1 staining on tumor cells and the likelihood of tumor regression following treatment with nivolumab existed with a two-sided p-value of 0.0476 by Fischer's exact test [17].

Therefore, PD-L1 expression levels will be measured in MEL and NSCLC tumor tissues by immunohistochemistry (IHC) performed on tumor tissue on glass slides. Statistical details for the biomarker analyses are described in Section 3.5 (Statistical Analysis Plan).

Other candidate biomarkers which will be investigated in the study may include, but are not limited to, the following:

- PD-L2 expression levels and TILs in biopsy tissue
- RNA and DNA profiling in biopsy tissue
- Quantitative RNA expression of candidate genes of interest (including PD-L1)
- Targeted and global proteomics in biopsy tissue
- Cytokine/chemokine profiles in peripheral blood
- Proteomics and RNA signature profiling in peripheral blood

3.4 SAFETY MEASUREMENTS

3.4.1 Clinical and Laboratory Measurements for Safety

Vital signs, weight, physical examinations, ECOG performance status, ECGs and laboratory safety tests (e.g., PT/aPTT, urinalysis, CBC, serum chemistries, auto-antibodies, thyroid function, viral antigen reactions, cytokine / chemokine panels) will be obtained and assessed at designated intervals throughout the study (see Study Flow Chart, Section 1.7). Special attention will be given to immune-related adverse events (e.g., gut, skin, liver, endocrine organs, others).

Adverse events will be graded and recorded throughout the study according to NCI-CTCAE, version 4.0. Characterization of toxicities will include severity, duration, and time to onset. Safety endpoints will include all types of adverse events, in addition to laboratory safety assessments, ECOG performance scale status, ECGs, and vital signs.

3.4.2 Recording Adverse Experiences

An adverse experience is defined as any unfavorable and unintended change in the structure, function, or chemistry of the body temporally associated with the use of the SPONSOR's product, whether or not considered related to the use of the product. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition which is temporally associated with the use of the SPONSOR's product, is also an adverse experience.

Changes resulting from normal growth and development which do not vary significantly in frequency or severity from expected levels are not to be considered adverse experiences. 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.

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

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

Progression of the cancer under study is not considered an adverse event unless it is considered to be drug related by the investigator.

All adverse events will be recorded from the time the consent form is signed through 30 days following cessation of treatment and at each examination on the Adverse Experience Case Report Forms/Worksheets.

3.4.3 Definition of an Overdose for This Protocol

Overdose is defined as:

The patient has taken (accidentally or intentionally) a dose exceeding the dose prescribed in the protocol by 20%.

3.4.3.1 Reporting of Overdose to SPONSOR

If an adverse experience(s) is associated with ("results from") the overdose of test drug or vaccine, the adverse experience(s) is reported as a serious adverse experience, even if no other criteria for serious are met.

If a dose of test drug 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 experience must be reported within 24 hours to one of the individuals listed on the sponsor contact information page found in the Administrative Binder.

3.4.4 Reporting of Pregnancy to SPONSOR

Although not considered an adverse experience, it is the responsibility of investigators or their designees to report any pregnancy in a subject/patient or a male patient's partner (spontaneously reported to them) which occurs during the study or within 120 days of completing the study. All subjects/patients who become pregnant must be followed to the completion/termination of the pregnancy. If the pregnancy continues to term, the outcome (health of infant) must also be reported to one of the individuals listed on the SPONSOR Contact Information page found in the Administrative Binder.

3.4.5 Immediate Reporting of Adverse Experiences to the SPONSOR

Any serious adverse experience should be recorded and reported within 24 hours to the SPONSOR via facsimile (found in the administrative binder).

3.4.5.1 Serious Adverse Experiences

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

1. Results in death;
2. Is life threatening;
3. Results in persistent or significant disability/incapacity;
4. Results in or prolongs an existing inpatient hospitalization;
5. Is a congenital anomaly/birth defect;
6. Is a new cancer (that is not a condition of the study);
7. Is associated with an overdose;

8. Is an other important medical event

Refer to Table 3-3 for additional details regarding each of the above criteria.

Any serious adverse experience, including death due to any cause other than progression of the cancer under study, which occurs to any subject/patient entered into this study or within 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, whether or not related to the investigational product, must be reported within 24 hours to one of the individual(s) listed on the contact information page.

Additionally, any serious adverse experience considered by an investigator who is a qualified physician to be possibly, probably, or definitely related to the investigational product that is brought to the attention of the investigator at any time outside of the time period specified in the previous paragraph also must be reported immediately to one of the individuals listed on the sponsor contact information page found in the administrative binder.

All subjects/patients with serious adverse experiences must be followed up for outcome.

3.4.6 Evaluating Adverse Experiences

An Investigator, who is a qualified physician, will evaluate all adverse experiences according to the NCI CTCAE, version 4.0. Any adverse experiences which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the adverse experience case report form.

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

Refer to Table 3-3 for instructions in evaluating adverse experiences.

Table 3-3

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

V 4.0 CTCAE Grading	**Grade 1**	**Mild; asymptomatic or mild 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 of hospitalization indicated; disabling; limiting self care ADL.**
	Grade 4	**Life threatening consequences; urgent intervention indicated.**
	Grade 5	**Death related to AE.**
	†Results in death; or	
	†Is life threatening; or places the subject/patient, in the view of the investigator, at immediate risk of death from the experience as it occurred [Note: This does not include an adverse experience that, had it occurred in a more severe form, might have caused death.]; or	
	†Results in a persistent or significant disability/incapacity (substantial disruption of one's ability to conduct normal life functions); or	
	†**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization [including hospitalization for an elective procedure] for a preexisting condition which has not worsened does not constitute a serious adverse experience.); or	
	†**Is a congenital anomaly/birth defect** (in offspring of subject/patient taking the product regardless of time to diagnosis); or	
	Is a new cancer; (that is a condition of the study) or	
	Is an overdose (Whether accidental or intentional.) Any overdose whether or not associated with an adverse experience 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 experience when, based upon appropriate medical judgment, the event may jeopardize the subject/patient 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 experience. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the adverse experience cause the test drug to be discontinued?	
Relationship to test drug	Did the test drug cause the adverse experience? The determination of the likelihood that the test drug caused the adverse experience 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 experience based upon the available information. **The following components are to be used to assess the relationship between the test drug and the AE;** the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the test drug caused the adverse experience (AE):	

Relationship to test drug (continued)	**The following components are to be used to assess the relationship between the test drug and the AE: (continued)**	
	Exposure	Is there evidence that the subject/patient was actually exposed to the test drug 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 test drug? Is the time of onset of the AE compatible with a drug-induced effect?
	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
	Dechallenge	Was the dose of test drug discontinued or 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 test drug; or (3) the study is a single-dose drug study.)
	Rechallenge	Was the subject/patient reexposed to the test drug 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 study is a single-dose drug study.) NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY THE TEST DRUG, OR IF REEXPOSURE TO THE TEST DRUG POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE SUBJECT/PATIENT, THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE U.S. CLINICAL MONITOR AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL.
	Consistency with Study Drug Profile	Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the test drug 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 drug relationship).**
Yes, there is a reasonable possibility of drug relationship.		There is evidence of exposure to the test drug. The temporal sequence of the AE onset relative to the administration of the test drug is reasonable. The AE is more likely explained by the test drug than by another cause. **Depending on data collection method employed, drug relationship may be further graded as follows:**
	Definitely related	There is evidence of exposure to the test drug. The temporal sequence of the AE onset relative to administration of the test drug is reasonable. The AE is more likely explained by the test drug than by another cause. Dechallenge is positive. Rechallenge (if feasible) is positive. The AE shows a pattern consistent with previous knowledge of the test drug or test drug class.
	Probably related	There is evidence of exposure to the test drug. The temporal sequence of the AE onset relative to administration of the test drug is reasonable. The AE is more likely explained by the test drug than by another cause. Dechallenge (if performed) is positive.
	Possibly related	There is evidence of exposure to the test drug. The temporal sequence of the AE onset relative to administration of the test drug is reasonable. The AE could have been due to another equally likely cause. Dechallenge (if performed) is positive.
No, there is not a reasonable possibility of drug relationship		Subject did not receive the test drug OR temporal sequence of the AE onset relative to administration of the test drug is not reasonable OR there is another obvious cause of the AE. (Also entered for a subject with overdose without an associated AE.) **Depending on data collection method employed, drug relationship may be further graded as follows:**
	Probably not related	There is evidence of exposure to the test drug. There is another more likely cause of the AE. Dechallenge (if performed) is negative or ambiguous. Rechallenge (if performed) is negative or ambiguous.
	Definitely not related	The subject/patient did not receive the test drug. OR Temporal sequence of the AE onset relative to administration of the test drug is not reasonable. OR There is another obvious cause of the AE.

3.4.7 SPONSOR Responsibility for Reporting Adverse Experiences

All adverse experiences will be reported to regulatory agencies, IRB/IECs, and investigators in accordance with all applicable global laws and regulations.

3.4.8 Events of Clinical Interest

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 Administrative Binder, or equivalent).

Following the guidelines described in Section 3.2.5.4.10.2, certain irAEs and AEs should also be reported to the SPONSOR as ECIs. Depending on the type and severity of an ECI, oral or intravenous treatment with a corticosteroid should be considered, in addition to appropriate symptomatic treatment of a given condition.

All ECIs should be reported to the SPONSOR within 24 hours or, at least, on the following working day to the SPONSOR via facsimile (documentation is found in the Administrative Binder).

3.4.9 Protocol-Specific Exceptions to Serious Experience Reporting

Efficacy endpoints outlined in this section will not be reported to the Sponsor as described in Section 3.4.5. Immediate Reporting of Adverse Experiences to the Sponsor except as follows:

- If a serious and unexpected adverse experience occurs for which there is evidence suggesting a causal relationship between the drug and the event, the event must also be reported as a serious and unexpected suspected adverse reaction within 24 hours to the Clinical Monitor either by electronic media or paper even if it is a component of the study endpoint (e.g., all-cause mortality).

Specifically, the suspected/actual events (as opposed to endpoints or endpoint components) covered in this exception are as follows: hospitalization or death due to progression of the cancer under study. Note: As described in Section 3.4.5.1, any secondary primary cancer needs to be reported as an SAE.

For this protocol, the Following MedDRA Preferred Terms are considered suspected efficacy endpoint/endpoint events:

- Disease Progression
- Malignant Neoplasm Progression

The Sponsor will monitor unblinded aggregated efficacy endpoint event and other safety data including fatal events 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.

3.5 STATISTICAL ANALYSIS PLAN (SAP)

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, changes are made to primary, secondary or tertiary objectives and/or hypotheses, or to the statistical methods related to those objectives and/or hypotheses, then those changes, along with an explanation as to when and why they occurred, will be listed in the Clinical Study Report (CSR) for the study. Post hoc exploratory analyses will be clearly identified in the CSR. No separate Statistical Analysis Plan (SAP) will be issued for this study.

3.5.1 Responsibility for Analyses/In-House Blinding

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

This trial is being conducted as an open-label study (i.e., patients, investigators, and SPONSOR personnel will be aware of patient treatment assignments after each patient is enrolled and treatment is assigned). However, for those randomized cohorts, treatment assignment is based on an allocation schedule generated in-house to maintain randomness.

3.5.2 Hypotheses/Estimation

Objectives and hypotheses of the study are stated in Section 2.1.

The primary endpoint is RR based on RECIST 1.1 by blinded central reviewers for demonstrating the anti-tumor activity of MK-3475 in all populations (see hypotheses in Section 3.5.7). In addition, RR and DCR as assessed per irRC by investigators in the ipilimumab-naïve population treated at 10 mg/kg in Part B enrolled through Amendment 4 will be analyzed for internal decision purposes, and the study in this population is considered positive (i.e., demonstration of proof-of-concept) if the outcome in either endpoint is positive. The following table (Table 3-4) provides the target RR and DCR of interest for the ipilimumab-naïve population. The null hypothesis is derived from the published Phase III data on single agent ipilimumab [71], and the alternative hypothesis is derived from the nivolumab data as reported at the 2010 American Society of Clinical

Oncology (ASCO) meeting [74]. To properly reflect the preliminary nature of the nivolumab data, two effect sizes are considered for the alternative hypothesis (intermediate and high), with the high effect size representing the data as reported and the intermediate effect size representing a slightly lower efficacy size that is still considered of clinical interest.

Table 3-4

Target Response Rate (RR) and Disease Control Rate (DCR) of Interest in Ipilimumab-naïve Population

Hypotheses	Week 12		Overall	
	RR	DCR	RR	DCR
Null hypothesis	5%	30%	10%	30%
Alternative hypothesis (intermediate)	15%	45%	25%	50%
Alternative hypothesis (high)	20%	50%	30%	55%

An important secondary objective of study is to investigate the correlation between various candidate biomarkers and anti-tumor activity of MK-3475. The primary biomarker hypothesis to be tested in the study is that expression of PD-L1 in tumor tissue at baseline is concordant with anti-tumor activity, assessed as maximum total reduction (%) in tumor volume produced by MK-3475.

3.5.3 Analysis Endpoints

3.5.3.1 Efficacy Endpoints

RR and DCR will serve as primary efficacy endpoints only for the ipilimumab-naïve population treated at 10 mg/kg in Part B enrolled through Amendment 4 for internal decision purposes, and the study in this population is considered positive (i.e., demonstration of proof-of-concept in this population) if the outcome in either endpoint is positive. The recently published immune-related response criteria (irRC) as assessed by investigators will be applied as primary measure for assessment of tumor response [18]. RR and DCR will be also assessed based on RECIST 1.1 by blinded central reviewers as supportive analyses. Interim analyses will be based on RR and DCR at Week 12. Confirmation is required for final analysis of RR, but not for the interim analyses. Secondary efficacy endpoints for the above population will include duration of response, progression-free survival (PFS) and overall survival (OS). Response duration will be only determined for confirmed responses and is defined as the time from first documentation of response to first documentation of disease progression. PFS will be measured from start of treatment to documentation of definitive disease progression or death due to any cause, whichever occurs first. OS is defined as time from treatment initiation to death due to any cause.

The primary endpoint is RR to further demonstrate the anti-tumor activity of MK-3475 in all populations except as noted above. The primary measure for assessment of tumor response is based on RECIST 1.1 by blinded central reviewers and the secondary measure is based on irRC by investigators. DCR, response duration and PFS based on both irRC and RECIST 1.1, and OS will serve as secondary endpoints.

3.5.3.2 Safety Endpoints

The primary safety endpoint in Part A of the study is DLT. Other safety measures evaluated in all parts of the study are all other adverse events, laboratory safety assessments, ECGs, and vital signs.

3.5.3.3 Pharmacokinetic (PK) and Pharmacodynamic Endpoints

Blood samples for serum levels of MK-3475 and analysis of target engagement will be obtained at the time points listed in the Study Flow Chart, Section 1.7.

3.5.3.4 Predictive Biomarker Endpoints

The primary candidate biomarker to be investigated in this study is PD-L1 expression levels in tumor tissue at baseline, which will be assessed by IHC. Other candidate biomarkers which will be investigated include expression of PD-L2 and PD-1, RNA signature profiles, and quantitative RNA expression of candidate genes of interest, including PD-L1.

3.5.4 Analysis Populations

3.5.4.1 Efficacy Analysis

The primary efficacy analyses will be based on the Full Analysis Set (FAS) population. Patients with measurable disease at baseline, which is defined separately under investigator evaluation and central review, who received at least one dose of study treatment will be included in the FAS population. Analyses of PFS and OS are based on the APaT population that consists of all patients who received at least 1 dose of study treatment.

3.5.4.2 Safety Analysis

The All Patients as Treated (APaT) population will be used for the analysis of safety data in this study. The APaT population consists of all patients who received at least 1 dose of study treatment.

In order for a patient to be considered evaluable for the analysis of DLT, the patient must have either had a DLT in Cycle 1 or had received at least 90% of the prescribed dose of MK-3475 in Cycle 1 and completed all safety evaluations up to and including at least 28 days after the first administration of MK-3475 without experiencing a DLT. A patient without a DLT will replaced if he/she did not adequately complete the evaluation period associated with the first cycle of study therapy (i.e., discontinue prematurely due to a reason unrelated to study therapy) or if that patient received <90% of the prescribed dose.

3.5.4.3 Pharmacokinetic and Pharmacodynamic Analyses

Pharmacokinetic and pharmacodynamic analysis populations are defined separately for each parameter of interest, and include all evaluable patients for each. Factors such as age group and gender will also be explored.

3.5.4.4 Predictive Biomarker Analyses

The primary predictive biomarker analyses are based on evaluable patients with both a valid PD-L1 expression measurement and at least one disease assessment post-treatment. Patients with MEL will be evaluated separately from patients with NSCLC. Different cutoff points may be applied to different tumor types.

Exploratory analyses of other candidate predictive biomarkers will be conducted similarly.

3.5.5 Statistical Methods

3.5.5.1 Efficacy Analysis

Part A: Patients' best tumor response along with tumor type and other baseline characteristics will be listed.

Part B ipilimumab-naïve treated at 10 mg/kg enrolled through Amendment 4: Overall response rate (RR) and disease control rate (DCR) will be used as endpoints for efficacy assessment for internal decision purpose. A 95% confidence interval along with a one-sided p-value for testing the null hypothesis based on the binomial distribution will be provided for each for the two primary endpoints: overall RR and overall DCR. Similar analyses will be provided for interim analyses of RR and DCR at week 12. Exploratory analyses will be conducted to compare the PFS rate at 6-month and OS rate at 1-year with historical control as well as with the recent ipilimumab data adjusted with baseline factors such as ECOG [75].

RR will be the primary endpoint for efficacy assessment in all populations. The primary assessment is based on RECIST 1.1 by blinded central reviewers, and the secondary assessment is based on irRC by investigators. A 95% confidence interval for RR will be provided for each population and by dose/schedule as applicable. Although DCR is not the primary endpoint, similar analyses will also be provided. In addition, Kaplan-Meier plots and descriptive statistics of progression-free-survival (PFS) and overall survival (OS) will be provided. Further, in order to adjust for inadequate follow-up, Kaplan-Meier plot and descriptive statistics of time-to-response will be provided whereas the Kaplan-Meier estimate of cumulative response rate at the longest follow-up time-point will serve as an estimate of the overall response rate. Response rate based on patients with at least 28 weeks of follow-up will also be provided as an approximate of the overall response rate. Descriptive statistics will also be provided for analysis of response duration and tumor volumetric change. Between-treatment comparisons will be conducted for all efficacy endpoints as appropriate to investigate the dose/schedule difference.

3.5.5.2 Pharmacokinetic Analysis

MK-3475 PK variables (e.g., C_{max}, T_{max}, C_{trough} and AUC) will be calculated as appropriate and summary statistics will be provided. Graphical, non-compartmental and potentially exploratory compartmental analyses will be used for the analysis of the PK data. An exploratory analysis of a potential relationship between dose level, PK variables and clinical safety and anti-tumor activity will be performed as appropriate.

3.5.5.3 Pharmacodynamic Analysis

Summary statistics will be provided for PD-1 receptor occupancy and PD-1 target modulation. An exploratory analysis of a potential PK-PD relationship will be performed as appropriate.

3.5.5.4 Predictive Biomarker Analyses

MEL Patients

To address the primary predictive biomarker hypothesis in the MEL population, the following two-step approach will be implemented: 1) estimation of a cutoff point for PD-L1 expression level based on a training set of melanoma patients, and 2) application of the cutoff point to prospectively test the biomarker hypothesis (i.e., formal validation of the cutoff point). The training set consists of patients from the cohort B enrolled through Amendment 04, including 20 ipi-naïve patients at 2 mg Q3, 22 ipi-naïve patients at 10 mg Q3, 41 ipi-naïve patients at 10 mg Q2, 32 ipi-treated patients at 10 mg Q3, and 16 ipi-treated patients at 10 mg Q2. Once the cutoff point is estimated, it will be applied to the analysis of randomized patients in Part B and Part D.

The cutoff point determination process is blinded to the validation analyses to ensure they have the necessary scientific rigor and integrity to confirm a clinical benefit of MK-3475 in the “biomarker positive" patients.

Estimation of cutoff point

All patients in the training set are required to have new biopsies such that we expect the yield of tumor samples available for PD-L1 analysis to be very close to the number of patients enrolled. All tumors will be tested retrospectively, with the test operators blinded to all clinical data. Four scoring systems will be evaluated initially: one based on H-score, the other three based on the percentage of tumor cells expressing PD-L1 with minimum intensities of 1+, 2+, and 3+, respectively. The latter two scoring systems (percentage of tumor cells with minimum intensities of 2+ or 3+) may be abandoned if the operators determine that they are too difficult to score.

Kendall's tau statistic along with a one-sided p-value will be provided for testing the concordance between maximum total tumor volume reduction (%) produced by MK-3475 and PD-L1 expression levels in tumor tissue [20]. Kendall's tau statistic is rank based. For the supportive analysis, those without a post-treatment disease assessment (presumably mainly due to discontinuation before week 12) will be assigned a

lower rank (equivalent to less tumor reduction) than those with a post-treatment disease assessment. They will further be ranked by category of reasons for discontinuation (death, disease progression by RECIST 1.1 per central review and other reasons) in ascending order, and among each category they will be ranked by time to discontinuation, the earlier the lower. Supportive analysis will be performed assessing the concordance between response by RECIST 1.1 per central review and PD-L1 expression.

Receiver operating characteristic (ROC) analysis will be generated for each scoring system. The cutoff point will be chosen by statistical estimation of Youden Index assisted with visual inspection from the ROC. In addition, the following two confounding categorical variables will be evaluated to determine whether or not they can be used to further improve the scoring system: "stroma pattern" (presence or absence of a band mononuclear inflammatory cells expressing PD-L1, in the stroma adjacent to tumor nests) and "dendritic pattern" (presence or absence of a lattice of dendritic cells expressing PD-L1, within tumor nests). Once the final scoring system and cutoff point is chosen, it will be documented before validation can be conducted.

Validation

Tumor samples from patients in the validation sets will be sent to a third party contract research organization (CRO) for re-identification. The CRO will remove old identifying information from each sample and replace it with a new identifier. The samples will then be sent to the clinical laboratory sites for analysis. Thus, both Merck and the laboratories will be blinded to the linkage between PD-L1 test result and the clinical outcome. The third-party CRO will release the key containing the old versus new identifiers to Merck only after database lock.

Patients with PD-L1 expression level above the final cutoff point will be analyzed by dose/schedule, separately for the ipi-refractory population and the ipi-naïve population. Based upon current data from this trial indicating similar response rates between ipi-naïve and ipi-treated patients, an analysis will also be performed where the two populations are combined for a given dose/schedule or even across doses/schedules as appropriate. RR, DCR and other efficacy endpoints will all be compared by PD-L1 expression category (above or below cutoff). A multivariate logistic regression analysis will be conducted to further assess the cutoff point after adjustment of important baseline characteristics. Covariates in the regression model will include PD-L1 expression category (above cutoff, below cutoff or indeterminate), gender, age category (above or below median), ECOG performance status (0 or 1), LDH (≤ upper limit of the normal range OR > upper limit of the normal range or unknown), baseline tumor volume (above or below median), number of previous systemic therapies (< or ≥ median) and other prognostic factors and predictive biomarkers as appropriate.

Indeterminate PD-L1 expression levels are presumed to be missing at random. Reasons of missing data will be listed and investigated. A supportive analysis will be conducted to include those patients suspected to violate the missing at random assumption. PD-L1

expressions levels for these patients will be conservatively imputed to appropriately penalize for possible informative missing data.

Part F 2L+ Patients

The randomization of the 250 2L+ patients may be stratified by PD-L1 expression level based on a preliminary cutoff point once available, mainly based on Part C data. Data based on the patients enrolled in the non-randomized portions of Part F (amendment 06) will be pooled with Part C data, some data from Part A, and possibly data from 1L patients in Part F (amendment 06), to determine the final cutoff point for patients with strongly positive tumors (the primary population in this cohort) using the same estimation methods as for the melanoma patients. Just like for the melanoma patients, the cutoff point is determined in isolation to the 250 patients enrolled in the randomized portion of Part F (amendments 07 and 08) to ensure that the subgroup analysis of the patients with strongly positive tumors is blinded to the determination process. Notice that the cutoff point is driven by patients on the Q3W schedule. To properly compare the difference (if any) in cutoff point between the two dose schedules, patients treated at 10 mg/kg Q2W will be divided into two sets with half in the training set and half in the validation set for estimation and validation of a cutoff point specifically for the Q2W schedule.

Enrollment of patients with weakly positive tumors will be capped at 50%. Besides, an interim analysis will be conducted to potentially exclude patients with weakly positive tumors (based on final cutoff point) from further enrollment (see Section 3.5.9 for details). Regardless, the final cutoff point, once determined, won't be changed for the primary analysis purposes to maintain the integrity of the analysis.

3.5.5.5 Safety Analysis

Safety and tolerability will be assessed by clinical review of all relevant parameters including DLTs, other AEs, laboratory tests, ECG measurements, and vital signs.

DLTs will be listed. At the end of the trial, a dose-response relationship for the rate of experiencing a DLT in Cycle 1 will be estimated using the pooling-of-adjacent-violators algorithm. This dose-safety estimation will be used to support determination of the MTD. The dose-response relationship, overall tolerability and safety profile, and the PK and pharmacodynamic data will inform the determination of a recommended Phase 2 dose.

The 80% confidence intervals and Bayes credible intervals for DLT and drug-related toxicity rates in Cycle 1 for an identified MTD level will be provided. Summary statistics (median and range) for time to onset of first drug-related toxicity in each dose level will be provided. Adverse experiences will be summarized as counts and frequencies for each dose level. Laboratory assessments, vital signs, and other safety endpoints will be summarized as appropriate.

3.5.6 Multiplicity

A Hochberg procedure will be applied to final analysis of RR and DCR for internal decision purposes based on the ipilimumab-naïve patients treated at 10 mg/kg in Part B enrolled through Amendment 4. The overall type I error rate is set at 5% (one-sided), i.e., the trial is considered to have reached the efficacy objective if the two corresponding p-values for testing the null hypothesis (RR=10% and DCR=30%) are less than 5% OR either one is less than 2.5%. There are two planned interim analyses for administrative purposes. There is no intention to terminate the study early for efficacy, and no multiplicity adjustment is applied to the interim analyses.

The predictive biomarker hypothesis on concordance between tumor volume change and PD-L1 will be formally tested at a type I error rate of 2.5% (one-sided) separately for each part of the study, irrespective of the outcome from efficacy analyses. Once the null hypothesis is rejected, a step-down procedure may be applied to the testing of other biomarker hypotheses prospectively specified before the end of the study. While additional exploratory analyses will be conducted to evaluate alternative predictive biomarkers, there is no multiplicity control of such analyses and no formal conclusion can be made.

The efficacy hypothesis on anti-tumor activity of MK-3475 is tested at 5% (one-sided) for Part B ipilimumab-treated (non-randomized), at 10% (one-sided) for Part C, and at 2.5% (one-sided) for all other populations. Between-dose comparisons are all conducted at 20% (two-sided), or equivalent 10% (one-sided) for sample size and power calculation purpose below, except for Part B (10 mg/kg Q3W vs 10 mg/kg Q2W) which is conducted at 5% (two-sided).

3.5.7 Sample Size and Power Calculations

Part B ipilimumab-naïve enrolled through Amendment 4 (non-randomized)

With 61 ipilimumab-naïve patients treated at the 10 mg/kg in both Q2W and Q3W, the study has approximately 97% power to detect an effect size of RR=25% or DCR=50% under the null hypothesis of RR=10% and DRC=30%, or >99% power to detect an effect size of RR=30% or DCR=55%, at a type I error rate of 5% (one-sided) based on the Hochberg procedure. For the subgroup of patients on a dose /schedule, the corresponding powers to the two effect sizes are respectively 87% and 97% when the sample size is 40, 76% and 91% when the sample size is 30, and 44% and 62% when the sample size is 15.

Part B ipilimumab-treated enrolled through Amendment 4 (non-randomized)

With 40 patients treated at 10 mg/kg, the study has approximately 92%/98% power to rule out a ≤5% spontaneous RR (null hypothesis) when the true RR is 20%/25% at the 5% type I error rate (one-sided). With true RR assumed to be 20%/25%, the corresponding power is 75%/90% when sample size is 30 and 59%/78% when sample size is 20 at Q3W or Q2W.

Part B ipilimumab-refractory enrolled after Amendment 04 (randomized: 10 mg/kg Q3W vs 2 mg/kg Q3W)

With 80 ipilimumab-refractory patients at each dose level, the study has ~85% (or 96%) power to detect a 15% (or 20%) difference in RR between the two doses at the 10% type I error rate (one-sided) when the RR in the inferior arm is 10%. A p-value of 10% approximately corresponds to a 7% empirical difference in RR.

In addition to detecting dose response, we are also interested in testing whether MK-3475 is superior to putative chemotherapies in this population. While the spontaneous RR is likely less than 5%, there is no historical data on response rate of chemotherapies in the ipilimumab-refractory population. However, it ranged from 5% to 10% for chemotherapies in three recently completed phase 3 studies (ipilimumab in 1st line melanoma patient, and trametinib and vemurafenib in patients with BRAF V600E mutation). Therefore, it is reasonable to use 10% as the null hypothesis for testing the anti-tumor activity of MK-3475 against putative chemotherapies in this population. With 80 patients treated at a dose level, the study has 93% power to reject the null hypothesis at a type I error rate of 2.5% (one-sided) when the true response rate of MK-3475 is 25%. A p-value of 2.5% approximately corresponds to a 19% empirical response rate when sample size is 80. With the prevalence of high PD-L1 projected to be from 40% to 60%, the number of high PD-L1 patients treated at a dose level ranges from 32 to 48 and the half-width of the 95% confidence intervals for RR at a dose level approximately ranges from 14% to 17% when the empirical RR in the high PD-L1 group is 50% and from 13% to 16% when the empirical RR in the high PD-L1 group is 70% or is 30%. With 32 to 48 patients in the PD-L1 high group, the study has 79% to 94% power to reject the null hypothesis of 10% RR at type I error rate of 2.5% (one-sided) when the true RR is 30%.

Part C NSCLC (single arm)

With 35 NSCLC patients treated at RP2D, the study has approximately 80% power to rule out a ≤9% RR (null hypothesis) when the true RR is 22% at the 10% type I error rate (one-sided).

Part D ipilimumab-naïve enrolled after Amendment 04 (randomized)

With 44 patients treated at 2 mg/kg and 44 treated at 10 mg/kg, the study has 80% power to detect 30% vs. 10% or 90% power to detect 25% vs 5% in RR between the two dose levels at the 10% type I error rate (one-sided). A p-value of 10% approximately corresponds to a 12% empirical difference in RR.

With 44 patients treated at a dose level, the study has 89% power to test the null hypothesis of RR=10% at 2.5% type I error rate (one-sided) when the true RR is 30%. A p-value of 2.5% approximately corresponds to an empirical RR of 23% (10/44).

Based on preliminary data from the non-randomized patients, the RR appears similar between the ipi-refractory population and the ipi-naïve population. A pooled analysis of the PD-L1 high patients from Part B (randomized) and Part D (randomized) will be

conducted. It is expected that 50-75 PD-L1 high patients will be treated at a dose level in the pooled analysis. With this sample size, the study has >95% power to reject the null hypothesis of 10% RR at type I error rate of 2.5% (one-sided) when the true RR is 30%.

Part B enrolled after Amendment 04 (randomized: 10 mg/kg Q3W vs 10 mg/kg Q2W)

A total of approximately 230 patients will be randomized 1:1 to 10 mg/kg Q3W or 10 mg/kg Q2W, stratified by ipi-naïve vs non ipi-naive. Based on preliminary data from non-randomized patients, the RR appears similar between the non ipi-naive population and the ipi-naïve population. The primary analysis of this cohort is based on a pooled analysis, stratified by ipilimumab treatment history. Subgroup analyses will also be conducted. With 230 patients, the study has ~85% power to detect a 20% difference (i.e., 30% vs 50%) in RR between the two doses at the 2.5% type I error rate (one-sided). A p-value of 2.5% approximately corresponds to a 13% empirical difference in RR.

Similar to randomized cohorts in Part B and Part D between 10 mg/kg Q3W vs 2 mg/kg Q3W, anti-tumor activities of MK-3475 at a dose schedule as well as related to PD-L1 expression will also be investigated.

Part F NSCLC 1L PD-L1 positive (randomized)

With 44 patients per dose level, the study has 86% power to detect a 25% difference in RR (i.e., 45% vs 20%) at alpha=10% (1-sided) between two dose levels. A p-value of 10% approximately corresponds to a 13% empirical difference in RR.

With 44 1L patients treated at a dose level, the study has 91% power to test the null hypothesis of RR=25% at 2.5% type I error rate (one-sided) when the true RR is 50%. A p-value of 2.5% approximately corresponds to an empirical RR of 41% (18/44).

Part F NSCLC 3L+ (single arm)

With 32 3L+ patients treated at 10 mg/kg, the study has 90% power to test the null hypothesis of RR=10% at 2.5% type I error rate (one-sided) when the true RR is 35%. A p-value of 2.5% approximately corresponds to an empirical RR of 25% (8/32).

Part F NSCLC 3L+ PD-L1 negative (single arm)

With 40 patients treated at 10 mg/kg Q2W, the study has >90% power to rule out a >30% RR if <8 patients respond (i.e., probability of observing < 8 responses is <10% when true RR is 30%).

Part F NSCLC 2L+ PD-L1 positive (randomized)

Approximately 250 patients will be randomized (3:2) to 10 mg/kg Q3W and 10 mg/kg Q2W. The randomization may be stratified by PD-L1 expression level based on a preliminary cutoff point once available (see Section 3.5.5.4 for details). With 250 patients, the study has approximately 95% power to detect a 15% difference in RR

between the two doses at type I error rate of 10% (one-sided) assuming that the RR at 10 mg/kg Q3W is 10%.

Enrollment of patients with weakly positive tumors will be capped at 50% so that at least 75 patients with strongly positive tumors will be treated at 10 mg/kg Q3W. With 75 patients treated at 10 mg/kg Q3W, the study has 85% power to detect a 15% difference in RR between MK-3475 and historical control which is conservatively estimated to be 15% (i.e., 30% vs 15%) at type I error rate of 2.5% (one-sided). A p-value of 2.5% approximately corresponds to an empirical RR of 25% (i.e., the lower bound of the 95% CI for an empirical RR at 25% will exclude 15%). With 50 patients at 10 mg/kg Q2W, the study has 68% (or 89%) power to detect a 15% (or 20%) difference in RR between MK-3475 and historical control at type I error rate of 2.5% (one-sided). A p-value of 2.5% approximately corresponds to an empirical RR of 28% (i.e., the lower bound of the 95% CI for an empirical RR at 28% will exclude 15%). If 10 mg/kg Q2W has comparable anti-tumor effect to 10 mg/kg Q3W in the population, the two doses will be pooled for a joint analysis as appropriate. Regardless, if the primary analysis in the biomarker strongly positive population is positive a step-down analysis will be performed to assess all biomarker positive patients including patients with weakly positive tumors.

If Part F data show no evidence that line of therapy (1L vs 2L+) impacts efficacy, data will be combined across line of therapy and within dose for more powerful assessment of difference in RR between the two dose schedules and for more precise estimation of RR at a dose schedule. The pooled analysis will be conducted in the overall biomarker positive population as well as in the strongly biomarker position population, as appropriate.

PD-L1 biomarker effect

Kendall's tau statistic will be used for testing the PD-L1 biomarker effect for various tumor and treatment groups. All testing will be conducted at type I error rate of 2.5% (one-sided). For a sample size of approximately 45 patients with both post-treatment disease assessments and valid evaluation of baseline PD-L1 expression levels in newly obtained tumor biopsies, the study has approximately 90% power to detect a one-fold difference in concordance (i.e., odds of concordance relative to discordance = 2, or in other words tumor is twice more likely to reduce than to increase if the patient’s tumor has high expression of the PD-L1 than low expression). When the sample size is reduced to 25 patients, Kendall's tau has 90% power to detect a 1.5 to 2-fold difference in concordance. In addition, the Youden index and other methods will be used for biomarker cut-off point analysis.

3.5.8 Subgroup Analyses and Effect of Baseline Factors

In assessment of anti-tumor activity in melanoma population, patients will be analyzed by treatment history with ipilimumab and by dose level and dosing interval (Q2W or Q3W). In addition, ipilimumab-naïve patients in Part B will be combined with those in Part D for a sensitivity analysis of treatment difference between the two doses. In assessment of

anti-tumor activity in NSCLC populations in Part C and Part F, patients will be analyzed by line of therapy and by dose level.

3.5.9 Interim Analyses

Part B Ipilimumab-Naïve Patients (non-randomized)

The study will have two planned interim analyses for internal decision purpose in ipilimumab-naïve patients treated at 10 mg/kg in Part B enrolled through Amendment 4 (non-randomized). The endpoints in these interim analyses are RR and DCR at week 12. There is no intention to stop the trial for efficacy at the first or second interim analysis. The accrual for Part B is expected to be fast. Should it be slower than expected, one additional interim analysis may be added. The decision rules at the interim analyses serve as guidance and are non-binding. In absence of a control arm, outcomes in this single arm study have to be interpreted with caution, both at interim and final analyses.

The first planned interim analysis will occur when the first 11 patients are evaluable for response assessment at 12 weeks (i.e., have either completed the first tumor re-assessment at week 12 or discontinued the study before week 12). To prevent undue over-enrollment in case the futility bar will be crossed and the study may get terminated early, enrollment of the first 13 MEL patients in Part B will be restricted to ipilimumab-naïve patients.

The futility bar has been set at zero objective response in 11 evaluable patients AND disease control in <5 patients at week 12. This decision criterion has 51% power to rule out the null hypothesis, 89% power to rule out the intermediate effect size and 95% power to rule out the high effect size.

Enrollment will not be stopped for purpose of the first interim futility analysis. Accordingly, approximately 30-38 patients may have been enrolled when the data from that analysis will become available, based on current accrual rate projections. This will include patients without and with prior treatment with ipilimumab.

If the futility bar will be crossed at the first futility analysis (i.e., in case of ≥1/11 responses OR ≥5/11 patients with disease control), enrollment will continue to the planned sample size for response assessment. If the futility bar will not be crossed at 11 patients, enrollment will be temporarily stopped until all patients who have been already enrolled at the time will have completed their week 12 disease assessment. The number of objective responses or disease control required in this second interim analysis to continue enrollment to the full planned sample size will depend on the number of available patients. In addition, preliminary biomarker data may be taken into account in the decision to continue or stop enrollment.

The second planned interim analysis will be performed when all patients have completed tumor assessment at Week 12 only if the primary objective of the analysis is not met earlier. The primary purpose of this analysis is to provide an early assessment of overall anti-tumor activity, for administrative purpose (e.g., planning of a subsequent study in

MEL). A Hochberg procedure with type I error rate of 5% (one-sided) will be applied to assist with the decision. Table 3-5 shows outcomes of interest that are on the borderline of the rejection zone of the null hypothesis, based on various hypothetical sample sizes of evaluable ipilimumab-naïve patients.

Table 3-5

Efficacy Outcome of Interest in Ipilimumab-Naïve Population
at the Second Planned Interim Analysis

Sample size	RR at week 12 (null=5%)		DCR at week 12 (null=30%)	
	Patients with response (%)	Nominal p-Value	Patients with disease control (%)	Nominal p-Value
25	4 (16%)	3.4%	12 (48%)	4.4%
30	5 (17%)	1.6%	14 (47%)	4.0%
35	5 (14%)	2.8%	16 (46%)	3.6%
40	6 (15%)	3.8%	18 (45%)	3.2%

As a comparison to interim analyses, Table 3-6 presents outcome of interest in the ipilimumab-naïve population at the final analysis based on various hypothetical sample sizes. For N varying from 30 to 45, an observed RR of approximately 20-23% OR a DCR of approximately 44-47% is generally required to cross the efficacy bar for a positive study (the bars will be lower when sample size is greater – data not shown in table). If the study objective is not met in the all-comer ipilimumab-naïve population, an exploratory analysis will be conducted in a "biomarker positive" subpopulation determined by the PD-L1 cut-off level. Such an analysis will be only performed if the primary biomarker hypothesis is confirmed, i.e., there will be statistical concordance between PD-L1 expression levels at baseline and maximum total tumor volume reduction (%) produced by MK-3475. A Hochberg procedure with type I error rate of 5% (one-sided) will be applied to assist with the analysis.

Table 3-6

Efficacy Outcome of Interest in Ipilimumab-Naïve Population at the Final Analysis

	Study RR (null=10%)		Study DCR (null=30%)	
	Patients with response (%)	Nominal p-Value	Patients with disease control (%)	Nominal p-Value
30	7 (23%)	2.6%	14 (47%)	4.0%
35	8 (23%)	2.0%	16 (46%)	3.6%
40	8 (20%)	4.2%	18 (45%)	3.2%
45	9 (20%)	3.2%	20 (44%)	2.8%

Part F 1L NSCLC PD-L1 positive Patients

For each dose level in Part F 1L, an interim analysis will be conducted after the first 20 patients have had a 3-month follow-up. The accrual to a dose level may be put on hold if ≤2 patients have a response. The probability of observing ≤2 responses out of 20 patients is <10% when the true RR is 25%. After a review of totality of data including tumor volumetric change, disease control rate and safety, the Sponsor will make a decision on whether to resume the accrual.

Part F 2L+ NSCLC PD-L1 positive Patients

There is one planned interim analysis. The primary objective of the interim analysis is to potentially exclude patients with weakly positive tumors (based on final cutoff point) from further enrollment. Based on current projection, the randomized portion may take 11 months to accrue. More interim analyses may be conducted if the accrual rate is slower than expected.

The interim analysis will be conducted after 60 patients in the randomized portion have a minimum follow-up of 12 weeks, which is expected to occur approximately 7 months after the randomization. The final PD-L1 assay cutoff point for efficacy analyses will be determined before this IA will occur. The target response rate is 20% for interim futility decisions. As guidance, if less than 3 out of 30 patients with weakly positive tumors (i.e., <10%) have a confirmed response no further patients with weakly positive tumors (based on final cutoff point) will be enrolled. The probability of observing less than 3 responses is <4% when the true response rate is 20%. When sample sizes are slightly different, an empirical response rate of <10% will be used as a reference or futility decisions which will also take into account the totality of data. Because the two dose schedules may have different cutoff points, a subgroup analysis by dose schedule will be conducted to determine whether to exclude patients with weakly positive tumors for one schedule or for both (see Section 3.5.5.4 for more details).

Additional Interim Analyses

In addition to the above interim analyses, an interim analysis of Part C may be conducted after all patients have had a 3-month follow-up, interim analyses of Part B ipilimumab-refractory patients and Part D ipilimumab-naive patients (timings to be determined) may be conducted to assist with the dose-selection decision for planning phase 2 studies in melanoma patients, and interim analyses may also be conducted to determine the cutoff points for high PD-L1 patients in melanoma and NSCLC patients (see Section 3.5.5.4).

3.6 LABELING, PACKAGING, STORAGE, DISPENSING, AND RETURN OF CLINICAL SUPPLIES

3.6.1 Patient and Replacements Information

MK-3475 clinical supplies will be packaged to support enrollment of approximately 1047 patients.

All other medications will be provided by the Investigator.

3.6.2 Product Descriptions

Investigational materials will be provided by the SPONSOR as summarized in Table 3-7.

Table 3-7

Product Descriptions

Product Name & Potency	Dosage Form
MK-3475 (SCH900475) 50 mg	Powder for injection

3.6.3 Primary Packaging and Labeling Information

MK-3475 (SCH900475) supplies will be packaged in **glass vials** as described in Table 3-8 below.

Table 3-8

Packaging of Clinical Supplies

Product Name & Potency	Fill Count	Dosing Instructions
MK-3475 (SCH900475)	50 mg/vial	Administer as directed

Container label text may include the following:

• Packaging Lot ID # • Fill Count & Dosage Form	• Dosing Instructions • Storage Conditions • Compound ID - Protocol # • Country regulatory requirements • SPONSOR address (If applicable)

3.6.4 Secondary Packaging and Labeling Information (kit)

Supplies may be packaged **in kit boxes containing 1 vial**. Kit configuration is subject to change as a result of packaging constraints.

If secondary packaging is utilized, label text may include the following:

• Packaging Lot ID # • Fill Count & Dosage Form	• Dosing Instructions • Storage Conditions • Compound ID - Protocol # • Country regulatory requirements • SPONSOR address (If applicable)

3.6.5 Clinical Supplies Disclosure

This study is open-label; therefore, the patient, the investigator's site personnel and the SPONSOR are not blinded to treatment. Drug identity (name, strength) is included in the label text; disclosure envelopes are not provided.

3.6.6 Storage and Handling Requirements

Clinical supplies should be kept in a secured location as indicated on the label. The clinical supplies storage area at the site must be monitored by the site staff for temperature consistency with the acceptable storage temperature range specified in this protocol or in the product label attached to the protocol. Documentation of temperature monitoring should be maintained.

3.6.7 Standard Policies / Return of Clinical Supplies

Investigational clinical supplies must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated personnel have access. Clinical supplies are to be dispensed only in accordance with the protocol. The investigator is responsible for keeping accurate records of the clinical supplies received from the SPONSOR, the amount dispensed to and returned by the subjects/patients, and the amount remaining at the conclusion of the study. In accordance with Good Pharmacy Practices, gloves should always be worn by study personnel if directly handling tablets or capsules that are returned (i.e., when

counting returns). The Clinical Monitor should be contacted with any questions concerning investigational products where special or protective handling is indicated. At the end of the study, all clinical supplies including partial and empty containers must be returned as indicated on the Contact Information page(s).

3.7 DATA MANAGEMENT

Information regarding Data Management procedures for this protocol will be provided by the SPONSOR.

3.8 BIOLOGICAL SPECIMENS

Information regarding biological specimens for this protocol will be provided by the SPONSOR.

4. ADMINISTRATIVE AND REGULATORY DETAILS

4.1 CONFIDENTIALITY

4.1.1 Confidentiality of Data

For Studies Conducted Under the U.S. IND

Particular attention is drawn to the regulations promulgated by the Food and Drug Administration under the Freedom of Information Act providing, in part, that information furnished to clinical investigators and Institutional Review Boards will be kept confidential by the Food and Drug Administration only if maintained in confidence by the clinical investigator and Institutional Review Board.

For All Studies

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, 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 study 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.

4.1.2 Confidentiality of Subject/Patient Records

For All Studies

By signing this protocol, the investigator agrees that the SPONSOR (or SPONSOR representative), Institutional Review Board/Independent Ethics Committee (IRB/IEC), or Regulatory Agency representatives may consult and/or copy study documents in order to verify worksheet/case report form data. By signing the consent form, the subject/patient agrees to this process. If study documents will be photocopied during the process of verifying worksheet/case report form information, the subject/patient will be identified by unique code only; full names/initials will be masked prior to transmission to the SPONSOR.

For Studies Conducted Under the U.S. IND

By signing this protocol, the investigator agrees to treat all patient data used and disclosed in connection with this study in accordance with all applicable privacy laws, rules and regulations, including all applicable provisions of the Health Insurance Portability and Accountability Act and its implementing regulations, as amended from time to time ("HIPAA").

4.1.3 Confidentiality of Investigator Information

For All Studies

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

- name, address, telephone number, and email address;
- hospital or clinic address and telephone number;
- curriculum vitae or other summary of qualifications and credentials; and
- 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 agencies or to other investigators. By signing this protocol, the investigator expressly consents to these uses and disclosures.

For Multicenter Studies
In order to facilitate contact between investigators, the SPONSOR may share an investigator's name and contact information with other participating investigators upon request.

4.2 COMPLIANCE WITH LAW, AUDIT, AND DEBARMENT

By signing this protocol, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol; 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 study.

The Code of Conduct, a collection of goals and considerations that govern the ethical and scientific conduct of clinical investigations sponsored by Merck, is attached.

The investigator also agrees to allow monitoring, audits, Institutional Review Board/ Independent Ethics Committee review, and regulatory agency inspection of trial-related documents and procedures and provide for direct access to all study-related source data and documents.

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

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

Study documentation will be promptly and fully disclosed to the SPONSOR by the investigator upon request and also shall be made available at the investigator's site upon request for inspection, copying, review, and audit at reasonable times by representatives of the SPONSOR or any regulatory agencies. 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 study documentation and worksheets/case report forms.

International Conference of Harmonization Good Clinical Practice guidelines (Section 4.3.3) 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.

According to European legislation, a SPONSOR must designate a principal or coordinating investigator (CI) to review the report (summarizing the study results) and confirm that to the best of his/her knowledge the report accurately describes conduct and results of the study. The SPONSOR may consider one or more factors in the selection of the individual to serve as the CI (e.g., thorough understanding of clinical trial methods, appropriate enrollment of subject/patient cohort, timely achievement of study milestones, availability of the CI during the anticipated review process).

The investigator will promptly inform the SPONSOR of any regulatory agency inspection conducted for this study.

Persons debarred from conducting or working on clinical studies by any court or regulatory agency will not be allowed to conduct or work on this SPONSOR's studies. The investigator will immediately disclose in writing to the SPONSOR if any person who is involved in conducting the study 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 site's IRB/IEC.

4.3 COMPLIANCE WITH FINANCIAL DISCLOSURE REQUIREMENTS

By signing this protocol, the investigator agrees to provide to the SPONSOR accurate financial information to allow the SPONSOR to submit complete and accurate certification and disclosure statements as required by U.S. Food and Drug Administration regulations (21 CFR Part 54). The investigator further agrees to provide this information on a Financial Disclosure/Certification Form that is provided by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. This requirement also extends to subinvestigators. The investigator also consents to the transmission of this information to Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

4.4 QUALITY CONTROL AND QUALITY ASSURANCE

By signing this protocol, the SPONSOR agrees to be responsible for implementing and maintaining quality control and quality assurance systems with written 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 study.

4.5 COMPLIANCE WITH INFORMATION PROGRAM ON CLINICAL TRIALS FOR SERIOUS OR LIFE THREATENING CONDITIONS

Under the terms of The Food and Drug Administration Modernization Act (FDAMA), the SPONSOR of the study is solely responsible for determining whether the study is subject to the requirements for submission to the Clinical Trials Data Bank, http://clinicaltrials.gov/. Merck, as SPONSOR of this study, will review this protocol and submit the information necessary to fulfill this requirement. Merck entries are not limited to FDAMA mandated trials. Merck's voluntary listings, beyond those mandated by FDAMA, will be in the same format as for treatments for serious or life-threatening illnesses. Information posted will allow patients to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate study locations and site contact information.

By signing this protocol, the investigator acknowledges that the statutory obligation under FDAMA is that of the SPONSOR and agrees not to submit any information about this study to the Clinical Trials Data Bank.

4.6 PUBLICATIONS

This study 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 study results within 12 months after the last data become available, which may take up to several months after the last patient visit in some cases such as vaccine trials. However, manuscript submission timelines may be extended on OTC studies. For studies intended for pediatric-related regulatory filings, the investigator agrees to delay publication of the study results until the SPONSOR notifies the investigator that all relevant regulatory requirements on the study drug have been fulfilled with regard to pediatric-related regulatory filings. Merck will post a synopsis of study results for approved products on www.clinicalstudyresults.org and www.clinicaltrials.gov by 12 months after the last patient's last visit or within 7 days of product approval in any major markets (United States, Europe or Japan), 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.

For multicenter studies, subsequent to the multicenter publication (or after public disclosure of the results online at www.clinicalstudyresults.org if a multicenter manuscript is not planned), an investigator and his/her colleagues may publish their data independently. In most cases, publication of individual site data does not add value to complete multicenter results, due to statistical concerns. In rare cases, publication of single site data prior to the main paper may be of value. Limitations of single 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 should meet conditions 1, 2, and 3. Significant contributions to study 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 study, final decisions on authorship and the order of authors' names will be made based on participation and actual contributions to the study and writing, as discussed above. The first author is responsible to defend 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 study 60 days prior to submission for publication/ presentation. Any information identified by the SPONSOR as confidential must be deleted prior to submission. SPONSOR review can be expedited to meet publication timelines.

5. LIST OF REFERENCES

1. Disis ML. Immune Regulation of Cancer. J Clin Oncol 2010;28:4531-8.

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

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

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

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

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

7. Nomi T, Sho M, Akahori T, Hamada K, Kubo A, Kanehiro, H, et al. Clinical significance and therapeutic potential of the programmed death-1 ligand/programmed death-1 pathway in human pancreatic cancer. Clin Cancer Res 2007;13:2151-7.

8. Gao Q, Wang XY, Qiu SJ, Yamato I, Sho M, Nakajima Y, et al. Overexpression of PD-L1 significantly associates with tumor aggressiveness and postoperative recurrence in human hepatocellular carcinoma. Clin Cancer Res 2009;15:971-9

9. Hamanishi J, Mandai M, Iwasaki M, Okazaki T, Tanaka Y, Yamaguchi K, et al. Programmed cell death 1 ligand 1 and tumor-infiltrating CD8+ T lymphocytes are prognostic factors of human ovarian cancer. Proc Natl Acad Sci USA 2007;104:3360-5.

10. Fourcade J, Kudela P, Sun Z, Shen H, Lenzner D, Guillaume P, et al. PD-1 is a regulator of NY-ESO-1-specific CD8+ T cell expansion in melanoma patients. J Immunol 2009;182:5240-9.

11. Cai G, Karni A, Oliveira EM, Weiner HL, Hafler DA, Freeman GJ. PD-1 ligands, negative regulators for activation of naive, memory, and recently activated human CD4+ T cells. Cell Immunol 2004;230:89-98

12. Blank C, Mackensen A. Contribution of the PD-L1/PD-1 pathway to T-cell exhaustion: an update on implications for chronic infections and tumor evasion. Cancer Immunol Immunother 2007;56:739-45.

13. Iwai Y, Ishida M, Tanaka Y, Okazaki T, Honjo T, Minato N. Involvement of PDL1 on tumor cells in the escape from host immune system and tumor immunotherapy by PD-L1 blockade. Proc Natl Acad Sci USA 2002;99:12293-7.

14. Tsushima, F, Tanaka, K, Otsuki, N, Youngnak, P, Iwai, H, Omura K, Azuma, M. Predominant expression of B7-H1 and its immunoregulatory roles in oral squamous cell carcinoma. Oral Oncol 2006;42:268-74.

15. Korman A, Chen B, Wang C, Wu L, Cardarelli J, Selby M. Activity of Anti-PD-1 in Murine Tumor Models: Role of "Host" PD-L1 and Synergistic Effect of Anti-PD-1 and Anti-CTLA-4. J Immunol 2007;178:abstr. 48.37.

16. Sznol M, Powderly JD, Smith DC, Brahmer JR, Drake CG, McDermott DF, et al. Safety and antitumor activity of biweekly MDX-1106 (anti-PD-1, BMS-936558/ONO-4538) in patients with advanced refractory malignancies. Proc Am Soc Clin Oncol 2010;28:abstr. 2506

17, Brahmer JR, Drake C, Wollner I, Powderly JD, Picus J, Sharfman WH, et al. Phase I study of single agent anti-programmed death-1 (MDX-1106) in refractory solid tumors: safety, clinical activity, pharmcodynamics, and immunologic correlates. J Clin Oncol 2010;28:3167-75.

18. Wolchok JD, Hoos A, O'Day S, Weber JS, Hamid O, Lebbe C, Maio M, Binder M, Bohnsack O, Nichol G, Humphrey R, Hodi FS. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. Clin Cancer Res 2009;Dec1;15(23):7412-20.

19. Hochberg Y. A sharper Bonferroni procedure for multiple tests of significance. Biometrika 1988;75:800–802.

20. Kendall M. A New Measure of Rank Correlation. Biometrika 1938;30:81-89.

21. Shirabe K, Motomura T, Muto J, Toshima T, Matono R, Mano Y, Takeishi K, Ijichi H, Harada N, Uchiyama H, Yoshizumi T, Taketomi A, Maehara Y. Tumor-infiltrating lymphocytes and hepatocellular carcinoma: pathology and clinical management. Int J Clin Oncol 2010 Oct 21.

22. Ruffell B, DeNardo DG, Affara NI, Coussens LM. Lymphocytes in cancer development: polarization towards pro-tumor immunity. Cytokine Growth Factor Rev 2010 Feb;21(1):3-10.

23. Bellati F, Visconti V, Napoletano C, Antonilli M, Frati L, Panici PB, Nuti M. Immunology of gynecologic neoplasms: analysis of the prognostic significance of the immune status. Curr Cancer Drug Targets 2009 Jun;9(4):541-65.

24. Delhem N, Carpentier A, Moralès O, Miroux C, Groux H, Auriault C, Pancré V. Regulatory T-cells and hepatocellular carcinoma: implication of the regulatory T lymphocytes in the control of the immune response. Bull Cancer 2008 Dec;95(12):1219-25.

25. Clark CE, Beatty GL, Vonderheide RH. Immunosurveillance of pancreatic adenocarcinoma: insights from genetically engineered mouse models of cancer. Cancer Lett 2009 Jun 28;279(1):1-7.

26. Nemolato S, Fanni D, Naccarato AG, Ravarino A, Bevilacqua G, Faa G. Lymphoepitelioma-like hepatocellular carcinoma: a case report and a review of the literature. World J Gastroenterol. 2008 Aug 7;14(29):4694-6.

27. Nobili C, Degrate L, Caprotti R, Franciosi C, Leone BE, Trezzi R, Romano F, Uggeri F, Uggeri F. Prolonged survival of a patient affected by pancreatic adenocarcinoma with massive lymphocyte and dendritic cell infiltration after interleukin-2 immunotherapy. Report of a case. Tumori 2008 May-Jun;94(3):426-30.

28. Piersma SJ, Welters MJ, van der Burg SH. Tumor-specific regulatory T cells in cancer patients. Hum Immunol 2008 Apr-May;69(4-5):241-9.

29. Talmadge JE, Donkor M, Scholar E. Inflammatory cell infiltration of tumors: Jekyll or Hyde. Cancer Metastasis Rev 2007 Dec;26(3-4):373-400.

30. Al-Shibli K, Al-Saad S, Andersen S, Donnem T, Bremnes RM, Busund LT. The prognostic value of intraepithelial and stromal CD3-, CD117- and CD138-positive cells in non-small cell lung carcinoma. APMIS 2010 May;118(5):371-82.

31. Rao UN, Lee SJ, Luo W, Mihm MC Jr, Kirkwood JM. Presence of tumor-infiltrating lymphocytes and a dominant nodule within primary melanoma are prognostic factors for relapse-free survival of patients with thick (t4) primary melanoma: pathologic analysis of the e1690 and e1694 intergroup trials. Am J Clin Pathol 2010 Apr; 133(4):646-53.

32. Shen Z, Zhou S, Wang Y, Li RL, Zhong C, Liang C, Sun Y. Higher intratumoral infiltrated Foxp3+ Treg numbers and Foxp3+/CD8+ ratio are associated with adverse prognosis in resectable gastric cancer. J Cancer Res Clin Oncol 2010 Oct; 136(10):1585-95.

33. Laghi L, Bianchi P, Miranda E, Balladore E, Pacetti V, Grizzi F, Allavena P, Torri V, Repici A, Santoro A, Mantovani A, Roncalli M, Malesci A. CD3+ cells at the invasive margin of deeply invading (pT3-T4) colorectal cancer and risk of post-surgical metastasis: a longitudinal study. Lancet Oncol 2009 Sep;10(9):877-84.

34. Li JF, Chu YW, Wang GM, Zhu TY, Rong RM, Hou J, Xu M. The prognostic value of peritumoral regulatory T cells and its correlation with intratumoral cyclooxygenase-2 expression in clear cell renal cell carcinoma. BJU Int 2009 Feb; 103(3):399-405.

35. Sasaki A, Tanaka F, Mimori K, Inoue H, Kai S, Shibata K, Ohta M, Kitano S, Mori M. Prognostic value of tumor-infiltrating FOXP3+ regulatory T cells in patients with hepatocellular carcinoma. Eur J Surg Oncol 2008 Feb;34(2):173-9.

36. Hillen F, Baeten CI, van de Winkel A, Creytens D, van der Schaft DW, Winnepenninckx V, Griffioen AW. Leukocyte infiltration and tumor cell plasticity are parameters of aggressiveness in primary cutaneous melanoma. Cancer Immunol Immunother 2008 Jan;57(1):97-106.

37. Gao Q, Qiu SJ, Fan J, Zhou J, Wang XY, Xiao YS, Xu Y, Li YW, Tang ZY. Intratumoral balance of regulatory and cytotoxic T cells is associated with prognosis of hepatocellular carcinoma after resection. J Clin Oncol 2007 Jun 20;25(18):2586-93.

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

39. Oshikiri T, Miyamoto M, Shichinohe T, Suzuoki M, Hiraoka K, Nakakubo Y, Shinohara T, Itoh T, Kondo S, Katoh H. Prognostic value of intratumoral CD8+ T lymphocyte in extrahepatic bile duct carcinoma as essential immune response. J Surg Oncol 2003 Dec;84(4):224-8.

40. Diederichsen AC, Hjelmborg JB, Christensen PB, Zeuthen J, Fenger C. Prognostic value of the CD4+/CD8+ ratio of tumour infiltrating lymphocytes in colorectal cancer and HLA-DR expression on tumour cells. Cancer Immunol Immunother 2003 Jul;52(7):423-8.

41. Usubütün A, Ayhan A, Uygur MC, Ozen H, Toklu C, Ruacan S. Prognostic factors in renal cell carcinoma. J Exp Clin Cancer Res 1998 Mar;17(1):77-81.

42. Diez M, Pollán M, Enriquez JM, Dominguez P, Santana A, Tobaruela E, Mugüerza JM, Arrieta F, Rodriguez A, Ruiz A. Histopathologic prognostic score in colorectal adenocarcinomas. Anticancer Res 1998 Jan-Feb;18(1B):689-94.

43. Ropponen KM, Eskelinen MJ, Lipponen PK, Alhava E, Kosma VM. Prognostic value of tumour-infiltrating lymphocytes (TILs) in colorectal cancer. J Pathol 1997 Jul;182(3):318-24.

44. Shirabe K, Motomura T, Muto J, Toshima T, Matono R, Mano Y, Takeishi K, Ijichi H, Harada N, Uchiyama H, Yoshizumi T, Taketomi A, Maehara Y. Tumor-infiltrating lymphocytes and hepatocellular carcinoma: pathology and clinical management. Int J Clin Oncol 2010 Dec;15(6):552-8.

45. Hiraoka N. Tumor-infiltrating lymphocytes and hepatocellular carcinoma: molecular biology. Int J Clin Oncol 2010 Dec;15(6):544-51.

46. Liotta F, Gacci M, Frosali F, Querci V, Vittori G, Lapini A, Santarlasci V, Serni S, Cosmi L, Maggi L, Angeli R, Mazzinghi B, Romagnani P, Maggi E, Carini M, Romagnani S, Annunziato F. Frequency of regulatory T cells in peripheral blood and in tumour-infiltrating lymphocytes correlates with poor prognosis in renal cell carcinoma. BJU Int 2011 May;107(9):1500-6.

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

48. Deschoolmeester V, Baay M, Van Marck E, Weyler J, Vermeulen P, Lardon F, Vermorken JB. Tumor infiltrating lymphocytes: an intriguing player in the survival of colorectal cancer patients. BMC Immunol 2010 Apr 12;11:19.

49. Pölcher M, Braun M, Friedrichs N, Rudlowski C, Bercht E, Fimmers R, Sauerwald A, Keyver-Paik MD, Kübler K, Büttner R, Kuhn WC, Hernando JJ. Foxp3(+) cell infiltration and granzyme B(+)/Foxp3(+) cell ratio are associated with outcome in neoadjuvant chemotherapy-treated ovarian carcinoma. Cancer Immunol Immunother 2010 Jun;59(6):909-19.

50. Suzuki H, Chikazawa N, Tasaka T, Wada J, Yamasaki A, Kitaura Y, Sozaki M, Tanaka M, Onishi H, Morisaki T, Katano M. Intratumoral CD8(+) T/FOXP3 (+) cell ratio is a predictive marker for survival in patients with colorectal cancer. Cancer Immunol Immunother 2010 May;59(5):653-61.

51. Chew V, Tow C, Teo M, Wong HL, Chan J, Gehring A, Loh M, Bolze A, Quek R, Lee VK, Lee KH, Abastado JP, Toh HC, Nardin A. Inflammatory tumour microenvironmentis associated with superior survival in hepatocellular carcinoma patients. JHepatol 2010 Mar;52(3):370-9.

52. Kloor M. Lymphocyte infiltration and prognosis in colorectal cancer. Lancet Oncol 2009 Sep;10(9):840-1.

53. Oble DA, Loewe R, Yu P, Mihm MC Jr. Focus on TILs: prognostic significance of tumor infiltrating lymphocytes in human melanoma. Cancer Immun 2009 Apr 2;9:3.

54. Uppaluri R, Dunn GP, Lewis JS Jr. Focus on TILs: prognostic significance of tumor infiltrating lymphocytes in head and neck cancers. Cancer Immun 2008 Dec 4;8:16.

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

56. Leffers N, Gooden MJ, de Jong RA, Hoogeboom BN, ten Hoor KA, Hollema H, Boezen HM, van der Zee AG, Daemen T, Nijman HW. Prognostic significance of tumor-infiltrating T-lymphocytes in primary and metastatic lesions of advanced stage ovarian cancer. Cancer Immunol Immunother 2009 Mar;58(3):449-59.

57. Al-Shibli KI, Donnem T, Al-Saad S, Persson M, Bremnes RM, Busund LT. Prognostic effect of epithelial and stromal lymphocyte infiltration in non-small cell lung cancer. Clin Cancer Res 2008 Aug 15;14(16):5220-7.

58. Galon J, Costes A, Sanchez-Cabo F, Kirilovsky A, Mlecnik, B, Lagorce-Pages C, Toslini M, Camus M, Berger A, Wind P, Zinzindohoue F, Bruneval P, Cugnenc P, Trajanoski Z, Fridman W, and Pages F. Type, density, and location if immune cells within human colorectal tumors predicts clinical outcome. Science 2006;313:1960-64.

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

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

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

62. Okazaki T, Maeda A, Nishimura H, Kurosaki T, Honjo T. PD-1 immunoreceptor inhibits B cell receptor-mediated signaling by recruiting src homology 2-domain-containing tyrosine phosphatase 2 to phosphotyrosine. Proc Natl Acad Sci USA 2001;98:13866-71.

63. Zhang X, Schwartz JC, Guo X, Bhatia S, Cao E, Lorenz M, et al. Structural and functional analysis of the costimulatory receptor programmed death-1. Immunity 2004;20:337-47.

64. Chemnitz JM, Parry RV, Nichols KE, June CH, Riley JL. SHP-1 and SHP-2 associate with immunoreceptor tyrosine-based switch motif of programmed death 1 upon primary human T cell stimulation, but only receptor ligation prevents T cell activation. J Immunol 2004;173:945-54.

65. Sheppard KA, Fitz LJ, Lee JM, Benander C, George JA, Wooters J et al. PD-1 inhibits T-cell receptor induced phosphorylation of the ZAP70/CD3zeta signalosome and downstream signaling to PKCtheta. FEBS Lett 2004;574:37-41.

66. Riley JL. PD-1 signaling in primary T cells. Immunol Rev 2009;229:114-25.

67. Parry RV, Chemnitz JM, Frauwirth KA, Lanfranco AR, Braunstein I, Kobayashi SV, et al. CTLA-4 and PD-1 receptors inhibit T-cell activation by distinct mechanisms. Mol Cell Biol 2005;25:9543-53.

68. Agata Y, Kawasaki A, Nishimura H, Ishida Y, Tsubata T, Yagita H, et al. Expression of the PD-1 antigen on the surface of stimulated mouse T and B lymphocytes. Int Immunol 1996;8(5):765-72.

69. Vibhakar R, Juan G, Traganos F, Darzynkiewicz Z, Finger LR. Activation induced expression of human programmed death-1 gene in T-lymphocytes. Exp Cell Res 1997;232:25-8.

70. Nishimura H, Honjo T, Minato N. Facilitation of beta selection and modification of positive selection in the thymus of PD-1-deficient mice. J Exp Med 2000;191:891-8.

71. Hodi FS, O'Day SJ, McDermott DF, Weber RW, Sosman JA, Haanen JB, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med 2010 Aug 19;363(8):711-23.

72. Robert C, Thomas L, Bondarenko I, O'Day S, et al. Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. N Engl J Med 2011 Jun 30;364(26): 2517-26.

73. Chapman PB, Hauschild A, Robert C, Larkin JM, Haanen JB, Ribas A, et al. Phase III randomized, open-label, multicenter trial (BRIM3) comparing BRAF inhibitor vemurafenib with dacarbazine (DTIC) in patients with ^{V600E}BRAF-mutated melanoma. 2011 ASCO Annual Meeting. J Clin Oncol 2011;29 (suppl; abstr LBA4).

74. Sznol M, Powderly JD, Smith DC, Brahmer JR, Drake CG, McDermott DF, et al. Safety and antitumor activity of biweekly MDX-1106 (Anti-PD-1, BMS-936558/ONO-4538) in patients with advanced refractory malignancies. 2010 ASCO Annual Meeting. J Clin Oncol 2010;28:15 (suppl; abstr 2506).

75. Korn EL, Liu PY, Lee SJ, Chapman JA, Niedzwiecki D, Suman VJ, et al. Meta-analysis of phase II cooperative group trials in metastatic stage IV melanoma to determine progression-free and overall survival benchmarks for future phase II trials. J Clin Oncol 2008 Feb 1;26(4):527-34.

76. Topalian SL, Hodi FS, Brahmer JR, Gettinger SN, Smith DC, McDermott DF, et al. Safety, Activity, and Immune Correlates of Anti-PD-1 Antibody in Cancer. N Engl J Med 2012 Jun 28;366:2443-2454.

77. Mu CY, Huang JA, Chen Y, Chen C, Zhang XG. High expression of PD-L1 in lung cancer may contribute to poor prognosis and tumor cells immune escape through suppressing tumor infiltrating dendritic cells maturation. Med Oncol 2011 Sep 28 (3):682-688.

78. Gettinger S, Horn L, Antonia SJ, Spigel DR, Gandhi L, Sequist LV, et al. Clinical Activity and Safety of Anti-Programmed Death-1 (PD-1) (BMS 936558/MDX-1106?ONO-4538) in Patients (Pts) with Advanced Non-Small Cell Lung Cancer (NSCLC). 2012 European Society for Medical Oncology Annual Meeting.

001-00

Phase I Study of Single Agent MK-3475 in Patients with Solid Tumors

Product: MK-3475
Protocol/Amendment No.: 001-00

THIS PROTOCOL AND ALL OF THE INFORMATION RELATING TO IT ARE CONFIDENTIAL AND PROPRIETARY PROPERTY OF MERCK SHARP & DOHME CORP., A SUBSIDIARY OF MERCK & CO., INC., WHITEHOUSE STATION, NJ, U.S.A.

SPONSOR:

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. (hereafter referred to as the **SPONSOR** or Merck)
One Merck Drive
P.O. Box 100
Whitehouse Station, NJ, 08889-0100, U.S.A.

Protocol-specific Sponsor Contact information can be found in the Administrative Binder.

TITLE:

Phase I Study of Single Agent MK-3475 in Patients with Solid Tumors

INVESTIGATOR:

PRIMARY:

CLINICAL PHASE: I

US IND NUMBER: 110,080

SITE:

INSTITUTIONAL REVIEW BOARD/ETHICS REVIEW COMMITTEE:

PROTOCOL

Phase I Study of Single Agent MK-3475 in Patients with Solid Tumors

TABLE OF CONTENTS

TABLE OF CONTENTS (CONT.)

TABLE OF CONTENTS (CONT.)

TABLE OF CONTENTS (CONT.)

TABLE OF CONTENTS (CONT.)

Product: MK-3475 1
Protocol/Amendment No.: 001-00

1. SUMMARY

1.1 TITLE

Phase I Study of Single Agent MK-3475 in Patients with Solid Tumors.

1.2 INDICATION

Patients with a histologically or cytologically confirmed diagnosis of melanoma (MEL) or any type of carcinoma who have progressive locally advanced or metastatic disease after failure of or intolerance to established standard medical anti-cancer therapies.

1.3 SUMMARY OF RATIONALE

Redacted

Redacted

1.4 SUMMARY OF STUDY DESIGN

This is a Phase I, open-label, non-randomized, cohort based dose escalation study of intravenous (IV) MK-3475 in patients with locally advanced or metastatic carcinomas or MEL. The study will use a modified 3+3 design based on the so-called toxicity probability intervals (TPI) method [18] and will have 2 parts. In the dose escalation part (Part A), cohorts of 3-6 patients will be enrolled sequentially at escalating doses of 1.0, 3.0 and 10 mg/kg. Dose escalation will continue until identification of a preliminary MTD, up to the highest planned dose of 10 mg/kg. In Part B, additional patients within 2 disease-specific cohorts (MEL and RCC) will be enrolled at the preliminary MTD to confirm the tolerability of the dose (dose confirmation part according to the TPI method), and for preliminary evaluation of anti-tumor activity in MEL and RCC.

1.5 SAMPLE

A maximum of approximately 32 eligible patients evaluable for safety and tolerability will be enrolled in this study, with approximately 18 patients in Part A and approximately 14 patients in Part B. Specifically, each disease-specific cohort of MEL and RCC in Part B will include approximately 7 patients.

In Part A, patients with a histological or cytological diagnosis of MEL or any type of carcinoma may be enrolled, and patients may have non-measurable disease. In Part B, only patients with MEL or RCC may be enrolled, and patients must have measurable disease as per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria (see Section 2.2 and Appendix 6.3).

To be eligible for the study, patients must be 18 years of age or older, must have metastatic disease or locally advanced disease not amenable to local therapy, and must have failed established standard medical anti-cancer therapies for a given tumor type or have been intolerant to such therapy, or in the opinion of the Investigator have been considered ineligible for a particular form of standard therapy on medical grounds. Patients must have an Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2.

1.6 DOSAGE/DOSAGE FORM, ROUTE, AND DOSE REGIMEN

MK-3475 will be administered as a 30 minute IV infusion. In Part A, three dose levels of MK-3475 will be evaluated: 1 mg/kg, 3 mg/kg and 10 mg/kg. To ascertain proper PK sampling and analysis, the interval between the first and second dose in Part A will be 28 days. In subsequent cycles the dosing interval will be 14 days. Patients in Part B will receive the preliminary MTD identified in Part A at a dosing interval of 14 days. Dose escalation in individual patients will not be permitted in this study.

1.7 STUDY FLOW CHART

	Screening [1] (-28 to -1 days)	Cycle 1 (28 Days)							Cycle 2 and Additional Cycles (14 Days ± 2 Days)	End of Study [2] (30 Days ± 3 Days after last dose)
Cycle Day		1	2	3	8	15	22	29 [3]	1	
Visit Number	1	2	3	4	5	6	7	8	N	
Study Procedures										
Informed Consent [4]	X									
Inclusion/Exclusion Criteria	X									
Demographics/Medical History/ Prior Medications [5]	X									
Vital Signs/Weight [6]	X	X				X		X	X	X
Physical Examination	X					X		X	X	X
ECOG Performance Status	X							X	X	X
12-Lead ECG [7]	X	X				X		X	X	X
Review Adverse Events [8]		X			X	X	X	X	X	X
Review Concomitant Medications		X			X	X	X	X	X	X
CBC with Differential [9]	X	X				X		X	X	X
Comprehensive Serum Chemistry Panel [9]	X	X				X		X	X	X
Coagulation Parameters [9,10]	X									X
Urinalysis [9]	X	X				X		X	X	X
Urine or Serum β-HCG [9,11]	X									
Lymphocyte subtyping (FACS) [12]		X	X	X	X	X	X	X	X	

	Screening [1] (-28 to -1 days)	Cycle 1 (28 Days)							Cycle 2 and Additional Cycles (14 Days ± 2 Days)	End of Study [2] (30 Days ± 3 Days after last dose)
Cycle Day		1	2	3	8	15	22	29 [3]	1	
Visit Number	1	2	3	4	5	6	7	8	N	
Study Procedures										
Thyroid Function [9,13]		X							X	X
Immunoglobulins [9,14]		X						X	X	
Viral Antigen Recall Reactions [15]		X		X	X	X	X	X		
Cytokine/Chemokine Panel [16]		X							X	
Auto-Antibodies [9,17]		X							X	X
Auto-MK-3475 Antibodies [18]		X							X	X
Proteomics in Blood [19]		X							X	
RNA Signature in Profiling in Blood [19]		X							X	
Pharmacodynamics [20]		X	X		X			X	X	X
Pharmacokinetics [20]		X	X	X	X	X	X	X	X	X
Efficacy Measurements										
Serum Tumor Markers (if appropriate) [9,21]	X								X	X
Tumor Imaging [22]	X								X	X
Drug Administration										
Study Drug Administration (30 minute infusion)		X							X	
Tumor Biopsies (Optional)										
Archival Tumor Tissues [23] (additional consent required)	X									
Fresh Tumor Biopsies [24] (additional consent required)	X								X	

1 Routine laboratory tests (serum chemistry; hematology) for screening should be performed within 10 days of enrollment.
2 End of Study visit should be conducted approximately 4 weeks after the last dose of study therapy or before the initiation of a new treatment, whichever comes first. Patients who are discontinued from the study due to an unacceptable drug-related adverse event will be followed until the resolution of the AE to Grade 0-1 or stabilization or until beginning of a new therapy for their cancer, whichever occurs first. In patients who discontinue before 24 months of study therapy and have no documented disease progression, every effort should be made to follow the patient (1) for approximately 6 months without disease progression, (2) until start of a new anti-cancer treatment, (3) until documented disease progression, or (4) until death, whichever occurs first. The interval of imaging studies should follow the guidelines as described in footnote 22 below.
3 Day 29 sample = predose for Cycle 2/Day 1 for patients continuing in the study.
4 Written consent must be obtained prior to performing any protocol specific procedure. Results of a test performed as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame (e.g. within 28 days prior to Cycle 1, Day 1). Assign Baseline number when the study informed consent is signed.
5 Includes history of treatment for the primary diagnosis, including prior systemic, radiation treatment and surgical treatment. Time of last prior cancer treatment must be documented. Radiographic studies performed prior to study entry may be collected for review by the investigator. Report complete medication history for 30 days prior to the screening visit (Visit 1).
6 Vital signs to include temperature, pulse, respiratory rate and blood pressure.
7 Electrocardiogram (ECG) should be performed pre and post infusion on Day 1 of each cycle. The ECG post infusion should be performed within +5 minutes following the completion of infusion.
8 Adverse experiences and laboratory safety measurements will be graded per NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. All adverse experiences, whether gradable by CTCAE or not, will also be evaluated for seriousness.
9 See Appendix 6.1 for list of laboratory tests. Routine laboratory tests (e.g., CBC with differential; comprehensive serum chemistry panel; PT/INR and aPTT; thyroid function tests such as T3, T4, TSH; immunoglobulins; auto-antibodies such as described in footnote 17; urinalysis; urine and serum β-HCG; tumor markers) will be performed by the local study site laboratory. Other laboratory tests will be performed by a central laboratory. Patient treatment and overall management decisions will be based on local laboratory data.
10 PT/INR and aPTT should be collected at baseline and at the mandatory safety follow-up visit after discontinuation of study therapy. Coagulation parameters should be determined throughout the study if clinically indicated.
11 For women of reproductive potential, a urine 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. Women who have been amenorrheaic for <2 years and who have not had a hysterectomy and oophorectomy will only be considered not to be of reproductive potential if they have a documented FSH value in the postmenopausal range.
12 Limited to Part A of the study: Cycle 1: predose; Days 3, 8, 15, 22 and 29; Cycle 2 and subsequently every other cycle in the first 12 months on study at predose.
13 T3, FT4, TSH; at every cycle.
14 Collection for analysis of IgG and IgM at baseline, in Part A on day 29 of Cycle 1, at predose every other cycle in first 12 months, approximately every 2 months in second 12 months, and at end of study visit
15 In Part A of the study: Cycle 1: predose; Days 3, 8, 15, 22 and 29.
16 Cycle 1: predose, 1 h +/- 30 minutes after end of infusion, and approximately 6 hours after start of infusion. Subsequently to be collected at predose approximately every month until 6 months of study therapy. Includes multi-analysis panels (MAPs): Cytokine MAPAv1.0 and MAPBv1.0, and OncologyMAPv1.0 from RulesBasedMedicine.
17 Collected at predose of Cycle 1 and Cycle 2, and then of every other cycle following Cycle 2. Include antinuclear antibodies; anti-DNA antibodies; antithyroglobulin antibodies; antimicrosomal antibodies; and anticardiolipin antibodies. When a blood sample is positive for antinuclear antibodies (i.e., titer of ≥40), it will be tested for antibodies against extractable nuclear antigens.
18 Collected at predose of Cycle 1 and Cycle 2, and then at predose of every other cycle. In patients who discontinue study therapy before 6 months, every effort should be made to analyze anti-MK-3475 antibodies approximately 6 months after the first dose.
19 Collected at baseline and every month at predose until 6 months of study therapy.
20 Refer to Details of Sampling for Pharmacokinetics and Pharmacodynamics flow chart for timing. Procedures for collection of samples are described in the procedures manual.
21 Tumor markers (if appropriate) will be collected within 14 days prior to Cycle 1/Day 1, and while on study approximately every 2 months in the first 12 months and approximately every 3 months in the 2nd year.

22	Tumor imaging (either CT or MRI, with preference for CT) will be performed within 30 days prior to enrollment, and while on study approximately every 2 months in the first 12 months and approximately every 3 months in the 2nd year. The same imaging technique should be used in a patient throughout the study. After first documentation of response (CR or PR) imaging performed at the next regularly scheduled time point (e.g., 2 months later in the first 12 months of study therapy) will be used for response confirmation. In patients with MEL and RCC who have measurable disease, response status will be assessed by the study site and by a central imaging vendor. The process for collection of CT images and transmission to the central vendor for purpose of central response review is described in the procedures manual.
23	Collection of archival tumor tissue for purpose of biomarker analysis. Access to archival tumor tissue is highly desirable but not mandatory. Specific instructions for tissue collection and shipment are provided in the procedures manual.
24	A fresh biopsy of a tumor lesion is desirable but not mandatory. Fresh biopsies should be limited to readily accessible tumor lesions (e.g., skin; peripheral lymph nodes; liver metastases which can be readily accessed using CT guidance). If performed, a tissue cylinder should be obtained that has proper size for histological examination and biomarker analysis (e.g., IHC of PD-1, PD-L1, PD-L2; RNA signature profiling). (See specific guidance for minimum needle gauge in the procedures manual.) When feasible, another tumor biopsy should be taken approximately 2 months after start of study therapy, to be able to compare the expression or profile of biomarkers while on study therapy versus baseline. Ideally, the follow-up biopsy should be taken from the same tumor lesion as the baseline biopsy.

Details of Sampling for Pharmacokinetics and Pharmacodynamics

	Screening (-28 to -1 days)	Cycle 1 [1] (28 Days)									Cycle 2 and Additional Cycles (14 Days ± 2 Days)		End of Study (30 Days ± 30 Days after last dose)
Cycle Day		1			2	3	8	15	22	29	1		
		Predose	Postdose								Predose	Postdose	
Time Points		-60 min to 0 h	+30 min[2]	6 h[3]	24 h[3]	48 h[3]					-60 min to 0 h	30 min[2]	
Pharmacokinetics		X	X	X	X	X	X	X	X	X[4]	X[5]	X[5]	X[7]
Pharmacodynamics: PD-1 Receptor Occupancy Assay		X			X		X			X[4]	X[6]		X[7]
Pharmacodynamics: PD-1 Target Modulation Assay		X			X		X			X[4]	X[6]		X[7]

Please note: Actual drug dosing and PK/PD sampling times have to be documented by the sites and will be captured in the database.

1 Cycle 1: Only patients in Part A of the study will have PK and PD blood samples collected at all time points. In Part B, PK and PD samples will be only collected at the predose and postdose time points.

2 Immediately at end of MK-3475 infusion. Allowable window is +5 minutes. Sample collection must be from opposite arm to that used for study drug infusion. If drug was administered via a central venous catheter, sample collection for PK should be from a different site.

3 Window: ±2 hours.

4 Day 29 sample = predose for Cycle 2/Day 1 for patients continuing in the study.

5 Cycle 2 and subsequently every other cycle during the first 12 months of study therapy.

6 Cycle 2 and subsequently every 4th cycle during the first 12 months of study therapy.

7 PK and both PD assays should be performed at the mandatory end of study visit.

2. CORE PROTOCOL

2.1 OBJECTIVES AND HYPOTHESES

2.1.1 Primary

1) Objective: To evaluate the tolerability of MK-3475 and to characterize the safety profile when administered as a single agent to adult patients with locally advanced or metastatic MEL or any type of carcinoma.

   Hypothesis: Intravenous administration of single agent MK-3475 will have acceptable safety and tolerability, and the overall data on dose limiting toxicity (DLT), MTD, safety profile, PK and PD will identify a dose of MK-3575 which is considered safe for evaluation in subsequent efficacy studies.

2.1.2 Secondary

1) Objective: To characterize the PK profile of single agent MK-3475.

2) Objective: To evaluate target engagement in peripheral blood (PD-1 receptor occupancy and modulation of receptor activity).

3) Objective: To explore the anti-tumor activity (response and response duration) of MK-3475 in malignant MEL and RCC.

2.1.3 Tertiary

1) Objective: To evaluate expression of various candidate biomarkers (e.g., PD-L1, PD-L2, PD-1; ribonucleic acid (RNA) signature profiles) and examine other tumor tissue characteristics (e.g., tumor infiltrating lymphocytes, macrophages) that may correlate with tumor response, and to evaluate potential differences between fresh tumor biopsies versus archival tumor samples from the same patients.

2) Objective: To evaluate potential differences in tumor tissue characteristics in biopsies taken during study therapy versus baseline.

3) Objective: To explore various candidate biomarkers in peripheral blood (e.g., lymphocyte subpopulations, proteomics, RNA signature profiles) that may correlate with tumor response when assessed at baseline or during therapy with MK-3475.

2.2 PATIENT INCLUSION CRITERIA

1) Patients must have a histological or cytological diagnosis of MEL or any type of carcinoma, progressive metastatic disease, or progressive locally advanced disease not amenable to local therapy:

- In Part A of the study, patients with MEL or any type of carcinoma are eligible for participation.

  i. Please note: tumor types of primary interest in this study are malignant MEL, RCC, hepatocellular carcinoma, non-small cell lung cancer, gastric carcinoma, ovarian carcinoma and colo-rectal carcinoma. These are the tumor types where clinical PD-1 inhibition has achieved objective tumor responses, or where high expression of PD-L1 or PD-L2 has been associated with poor prognosis.

- In Part B of the study, only patients with a histological diagnosis of malignant MEL or RCC are eligible for participation.

2) Patients must have failed established standard medical anti-cancer therapies for a given tumor type or have been intolerant to such therapy, or in the opinion of the Investigator have been considered ineligible for a particular form of standard therapy on medical grounds.

3) Measurable disease:

   - In Part A of the study, patients may have non-measurable disease.

   - In Part B of the study, patients must have measurable disease as defined per RECIST version 1.1 (Appendix 6.3):

     i. Tumor mass: Must be accurately measurable in at least 1 dimension (longest diameter to be recorded) with a minimum size of:

        a. 10 mm by computed tomography (CT) scan (CT scan slide thickness must be <5 mm),

        b. 10 mm caliper measurement by clinical examination (lesions which cannot be measured with caliper should be recorded as non-measurable),

        c. 20 mm by chest X-ray (if clearly defined and surrounded by aerated lung).

     ii. Malignant lymph nodes: >15 mm in **short** axis when assessed by CT scan (CT scan slice thickness must be <5 mm).

4) Patient is male or female and ≥18 years of age on day of signing informed consent.

5) Patient must have a performance status of ≤2 on the ECOG Performance Scale (Appendix 6.2).

6) Patient must have adequate organ function as indicated by the following laboratory values.

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1,500 /mcL
Platelets	≥100,000 / mcL
Hemoglobin	≥9 g/dL or ≥5.6 mmol/L– without qualifications
Renal	
Serum creatinine	≤1.5 X upper limit of normal (ULN)
Hepatic	
Serum total bilirubin	≤ 1.5 X ULN **OR** Direct bilirubin ≤ ULN for patients with total bilirubin levels > 1.5 ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 X ULN **OR** ≤ 5 X ULN for patients with active liver metastases
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT) Activated Partial Thromboplastin Time (aPTT)	≤1.5 X ULN ≤1.5 X ULN

7) Patient has voluntarily agreed to participate by giving written informed consent.

8) Female patient of childbearing potential has a negative urine or serum pregnancy test. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. The serum pregnancy test must be negative for the patient to be eligible.

9) Female patients enrolled in the study, who are not free from menses for >2 years, post hysterectomy / oophorectomy, or surgically sterilized, must be willing to use 2 adequate barrier methods of contraception to prevent pregnancy or to abstain from heterosexual activity throughout the study, starting with Visit 1 through 30 days after the last dose of study therapy. Approved contraceptive methods include for example; intra uterine device, diaphragm with spermicide, cervical cap with spermicide, male condoms, or female condom with spermicide. Spermicides alone are not an acceptable method of contraception.

   Male patients must agree to use an adequate method of contraception starting with the first dose of study drug through 90 days after the last dose of study therapy.

2.3 PATIENT EXCLUSION CRITERIA

A patient meeting any of the following criteria is not eligible to participate in this study:

1) Patient who has had chemotherapy, radioactive, or biological cancer therapy within 4 weeks prior to the first dose of study therapy, or who has not recovered to CTCAE grade 1 or better from the adverse events due to cancer therapeutics administered more than 4 weeks earlier.

2) Patient is currently participating or has participated in a study of an investigational agent or using an investigational device within 30 days of administration of MK-3475.

3) Patient is expected to require any other form of antineoplastic therapy while on study. Exempted are patients with prostate cancer who are on luteinizing hormone-releasing hormone (LHRH) agonists and continue on the same dose and type of LHRH agonists.

4) Patient is on chronic systemic steroid therapy at doses >10 mg/day, or on any other form of immunosuppressive medication.

5) Patient is on chronic anti-coagulation treatment with warfarin (Low molecular weight heparin or low dose aspirin are permitted).

6) Patient has a known history of a hematologic malignancy, primary brain tumor or sarcoma, unless the patient has undergone potentially curative therapy with no evidence of that disease for 5 years.

7) Patient has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Patients with previously treated brain metastases may participate provided they are clinically stable for at least 1 month prior to study entry, defined as: (1) no evidence of new or enlarging brain metastases and (2) off steroids, or on a stable dose of steroids for at least 1 month.

8) Patient had previously a severe hypersensitivity reaction to another mAb.

9) Patient has any active autoimmune disease or a documented history of autoimmune disease, except vitiligo or resolved childhood asthma/atopy.

10) Patient had prior therapy with an anti-PD-1 or anti-CTLA-4 antibody (or any other antibody targeting T cell co-stimulatory pathways).

11) Patient has an active infection requiring therapy.

12) Patient is known to be positive for Human Immunodeficiency Virus (HIV), Hepatitis B or Hepatitis C virus.

13) Patient has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the patient's participation for the full duration of the study, or is not in the best interest of the patient to participate, in the opinion of the treating Investigator.

14) Patient has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.

15) Patient is, at the time of signing informed consent, a regular user (including "recreational use") of any illicit drugs or had a recent history (within the last year) of substance abuse (including alcohol).

16) Patients with symptomatic ascites or pleural effusion. A patient who is clinically stable following treatment for these conditions (including therapeutic thoraco- or paracentesis) is eligible.

17) Patient is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the study.

2.4 STUDY DESIGN AND DURATION

2.4.1 Summary of Study Design

This is a Phase I, open-label, non-randomized, cohort based dose escalation study in patients with locally advanced or metastatic MEL or carcinoma. The study will use a modified 3+3 design based on the so-called TPI method [18] and has 2 parts. In Part A, cohorts of 3-6 patients with MEL or any type of carcinoma will be enrolled sequentially at escalating doses of 1.0, 3.0 and 10 mg/kg. Dose escalation will continue until identification of a preliminary MTD, up to the highest planned dose of 10 mg/kg. In Part B, additional patients within 2 disease-specific cohorts (MEL and RCC) will be enrolled at the preliminary MTD to confirm the tolerability of the dose (dose confirmation part according to the TPI method), and for preliminary evaluation of anti-tumor activity in MEL and RCC. The dose confirmation rules as described in Section 3.2.5.4.7 (dose confirmation part) will be applied in Part B. Patient enrollment at the preliminary MTD will continue until ≤3 of 14 patients experience a DLT (14 patients combined from Part A and B) or until a total of 14 patients within the 2 disease-specific cohorts have been enrolled (with 7 patients each for MEL and RCC), whichever occurs first. The primary data used for dose escalation and confirmation will be DLT in Cycle 1. (See Sections 3.2.5.4.7 for details regarding the TPI algorithm for dose escalation and confirmation.)

In Part A and B, patients may continue on study therapy up to 2 years from the start of treatment, as long as they have no tumor progression or other reasons for study discontinuation (Section 3.2.5.4.11). Patients may continue on study therapy beyond 2 years if the Investigator considers this to be in the best interest of the patient based on an assessment of clinical benefit and potential risks. Continuation of study therapy beyond 2 years has to be explicitly approved by the SPONSOR, and will be contingent on the continued availability of MK-3475 drug product. Efficacy and safety monitoring of these patients, including all laboratory analyses, will follow the guidelines for Cycle 2 and Additional Cycles as described in Section 1.7, Study Flow Chart.

The study will include PK measurements in every other treatment cycle during the first 12 months of study therapy, including multiple PK measurements in Cycle 1 of Part A.

Radiological assessment of tumor response status should be performed approximately every 2 months for the first 12 months of treatment and approximately every 3 months in the second year on study.

Patients will be monitored for safety, anti-MK-3475 antibodies and efficacy throughout the study. If available, archived tumor tissue will be collected for biomarker analysis. Fresh tumor biopsies may be performed for biomarker analysis in select patients with readily accessible tumor lesions. If feasible, another biopsy should be taken approximately 2 months after start of study therapy, to be able to compare the expression of biomarkers and other tumor tissue features on study drug versus baseline. Ideally, the follow-up biopsy should be taken from the same tumor lesion as the baseline biopsy.

2.4.2 Definition of Dose-Limiting Toxicities

All toxicities will be graded using National Cancer Institute (NCI) CTCAE Version 4.0 (Appendix 6.4). The occurrence of any of the following toxicities during Cycle 1 will be considered a DLT, if judged by the Investigator to be possibly, probably or definitely related to study drug administration:

1. Grade 4 non-hematologic toxicity.

2. Grade 3 non-hematologic toxicity lasting >3 days despite optimal supportive care.

    - Grade 3 fatigue will NOT be classified as DLT, irrespective of duration.

3. Any Grade 3 non-hematologic laboratory value if:

    - Medical intervention is required to treat the patient, or
    - The abnormality leads to hospitalization, or
    - The abnormality persists for >1 week.

4. Neutropenia that is:

    - Grade 3 or 4 (i.e., ANC <1000 per mm3) and associated with fever (oral temperature ≥39ºC) requiring antibiotic therapy.

    - Grade 4 which lasts >7 days or leads to use of therapeutic G-CSF

5. Grade 4 thrombocytopenia (i.e., platelets <25,000 per mm3) or Grade 3 thrombocytopenia (i.e., platelets <50,000 per mm3) with bleeding.

Patients who received <90% of the MK-3475 infusion in Cycle 1 (e.g., because the infusion had to be discontinued due to an infusion reaction) and did not experience a DLT will not be taken into account in the assessment of the overall DLT rate for the particular dose level cohort and need to be replaced.

If a patient experiences a DLT in Cycle 1, the patient will be discontinued from study therapy unless the Investigator considers it in the best interest of the patient to continue on study (e.g., in case of tumor regression, symptomatic disease improvement, and/or if the type of DLT is viewed as preventable in subsequent cycles, e.g., by premedication). Such cases will require approval by the SPONSOR prior to continuation on study therapy.

2.4.3 Treatment Plan

In Part A, the dosing interval between Cycle 1 and Cycle 2 of MK-3475 is 28 days. Further administrations of MK-3475 will be repeated every 14 days. Patients in Part B will receive MK-3475 every 14 days starting with Cycle 1. Dose escalation in individual patients will not be permitted.

In patients who have an adverse experience (AE) equivalent to the DLTs as described in Section 2.4.1., study therapy will be held until resolution of toxicity to Grade 0-1. In the event of insufficient resolution of toxicity 4 weeks after administration of study drug, study therapy will be discontinued. In patients who continue on study therapy after experiencing a DLT-type AE, the dosing interval in subsequent cycles will be increased to 3 weeks. Only 1 dosing delay due to toxicity will be permitted. In the event of a second occurrence of a toxicity which would require dosing delay, study therapy will be discontinued. (See Section 3.2.5.4.8 for detailed guidelines for dose modifications.)

Patients may continue on study therapy until disease progression, unacceptable toxicity, the withdrawal of consent, they require another form of cancer therapy as determined by the Investigator, they require >1 dosing delay of MK-3475 due to toxicity, or until 24 months from the time of enrollment (unless continuation beyond 2 years is explicitly approved by the SPONSOR, see Section 3.2.5.4.11 for further details). In Part A of the study, continuation of therapy after Cycle 1 will be at the discretion of the Investigator, based on tolerability and likelihood of clinical benefit.

The DETAILS portion of this document (Section 3) further outlines the treatment plan for the study, including permitted/prohibited medications and supportive care measures.

2.5 LIST OF EFFICACY/PHARMACOKINETIC/IMMUNOGENICITY MEASUREMENTS

The following evaluations will be performed throughout the course of the study:

- Tumor response assessments by physical examination and tumor imaging by CT or magnetic resonance imaging (MRI)
- Serum tumor markers (if applicable)
- Anti-MK-3475 antibodies

The following evaluations will be performed throughout the first 12 months of the study and at the end of study visit:

- PK measurements in serum
- PD measurements: PD-1 receptor occupancy and modulation of PD-1 receptor function
- Analysis of lymphocyte subpopulations (study Part A only)

The following evaluations will be performed throughout the first 6 months of the study:

- Chemokine/cytokine measurements in blood
- Proteomics and RNA signature profiling in blood

The Study Flow Chart (Section 1.7) provides specific details on collection time points. Details of collection procedures are found in the Procedures Manual for this study.

All the listed laboratory tests will be performed by a central laboratory with the exception of serum tumor markers. Details regarding the amount of blood to be drawn for PK, PD assays and the other specific blood tests conducted by a central laboratory, are provided in the Procedures Manual.

2.6 LIST OF SAFETY MEASUREMENTS

The following safety evaluations will be performed at baseline and throughout the course of the study:

- Vital signs
- Physical examinations
- Medical history
- Evaluation of AEs
- ECOG performance status
- Electrocardiogram (ECG)
- Laboratory tests: complete blood count (CBC), serum chemistry, urinalysis, pregnancy test (at screening and during study when clinically indicated), PT/aPTT (at screening, at the end of study visit, and during the study when clinically indicated)
- Thyroid function
- Auto-antibodies
- Immunoglobulins (IgG, IgM)

The following evaluations will be performed throughout the first 12 months of the study and at the end of study visit:

- Cytokine measurements
- Analysis of lymphocyte subpopulations

The following will be performed only in Cycle 1 of study Part A:

- Viral antigen recall reactions

Toxicity will be graded and recorded according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events-CTCAE, version 4.0 (http://ctep.cancer.gov).

Routine laboratory tests (e.g., CBC with differential; comprehensive serum chemistry panel; PT/INR and aPTT; thyroid function tests such as T3, T4, thyroid-stimulating hormone (TSH); immunoglobulins; auto-antibodies; urinalysis; urine and serum β-HCG) will be performed by the local study site laboratory. The other laboratory tests will be performed by a central laboratory. Patient treatment and overall management decisions will be based on local laboratory data. Details regarding the amount of blood drawn for testing to be conduced by a central laboratory are provided in the Procedures Manual.

2.7 STATISTICAL ANALYSIS PLAN SUMMARY

The primary purpose of this study is to investigate the safety and tolerability of MK-3475 administered intravenously to patients with locally advanced or metastatic MEL or carcinomas, and to characterize the PK profile. The preliminary efficacy of MK-3475 in MEL and RCC will also be explored.

Descriptive tables that summarize the number and percentage of patients that experience adverse events as categorized in the NCI CTCAE version 4.0 will be generated for the overall patient population, by MK-3475 dose level and for selected patient subsets.

At the end of the trial, the dose-safety relationship for the percentage of patients experiencing DLT in Cycle 1 will be estimated using all DLT data.

To investigate the preliminary efficacy of MK-3475, available data on tumor response and response duration (as assessed per RECIST criteria and by volumetric analysis) will be summarized overall and within the various dose levels.

MK-3475 PK samples will be assayed and PK parameters including, but not limited to, C_{max}, T_{max}, C_{trough} and AUC will be summarized using conventional techniques.

This study will enroll a maximum of approximately 32 patients who are evaluable for safety and tolerability.

Product: MK-3475 1
Protocol/Amendment No.: 001-00

3. PROTOCOL DETAILS

3.1 BACKGROUND/RATIONALE

Redacted

Product: MK-3475 2
Protocol/Amendment No.: 001-00

Redacted

Product: MK-3475 3
Protocol/Amendment No.: 001-00

Redacted

Redacted

3.2 STUDY PROCEDURES

3.2.1 Concomitant Medication(s)/Treatment(s)

All treatments that the Investigator considers necessary for a patient'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 study period, documentation of drug dosage, frequency, route, and date will also be included on the CRF.

All concomitant medications received within 14 days before the first dose of study mediation and 30 days after the last infusion of study medication should be recorded.

3.2.2 Prohibited Medications

Patients may receive other medications that the Investigator deems to be medically necessary, with the specific exception of non-protocol specified chemotherapy, radiotherapy, immunotherapy, anti-neoplastic biological therapy or investigational agents other than MK-3475. Patients who require the use of any of the aforementioned treatments for clinical management should be removed from the study. Patients with prostate cancer who have been on LHRH agonists before enrollment in this study may continue to stay on the same dosing regime of the particular LHRH agonist. Patients who require a change in dose, dosing interval, or in the type of LHRH agonist while on study should be removed from the study. Section 2.3 of the protocol (exclusion criteria) describes other medications which are prohibited in this study.

3.2.3 Diet/Activity

Patients should maintain a normal diet.

3.2.4 Pregnancy/Contraception/Nursing

3.2.4.1 Pregnancy Testing

All women who are being considered for participation in the study, and who are not surgically sterilized or postmenopausal, will be tested for pregnancy within 72 hours of receiving the first infusion of study medication. If a urine test if positive or borderline (unable to confirm as negative), a β-hCG test will be required. Patients must be excluded in the event of a positive or borderline test result. The results of the pregnancy test will not be recorded.

3.2.4.2 Contraception

MK-3475 may have adverse effects on a fetus *in utero*. Furthermore, it is not known if MK-3475 has transient adverse effects on the composition of sperm. Non-pregnant, non-breast-feeding women may be enrolled if they are considered highly unlikely to conceive. Highly unlikely to conceive is defined as 1) surgically sterilized, or 2) postmenopausal (a woman who is ≥45 years of age and has not had menses for greater than 2 years will be considered postmenopausal), or 3) not heterosexually active for the duration of the study, or 4) heterosexually active and willing to use 2 methods of birth control (recommended for the female partners of male patients). The 2 birth control methods can be 2 barrier methods *or* a barrier method plus a hormonal method to prevent pregnancy, used throughout the study starting with Visit 1 through 30 days after the last dose of study medication. Male patients enrolled in this study must also agree to use an adequate method of contraception starting with Visit 1 through 30 days after the last dose of study drug.

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

Patients should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study they must adhere to the contraception requirement (described above) for the duration of the study. If there is any question that a patient will not reliably comply with the requirements for contraception, that patient should not be entered into the study.

3.2.4.3 Use in Pregnancy

If a patient inadvertently becomes pregnant while on treatment with MK-3475, the patient will immediately be removed from the study. The site will contact the patient at least monthly and document the patient'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). If a male patient's partner becomes pregnant on study the pregnancy must be reported to the SPONSOR. The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the SPONSOR.

3.2.4.4 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, patients who are breast-feeding are not eligible for enrollment.

3.2.5 Procedures

3.2.5.1 Informed Consent

Study personnel must obtain documented consent from each potential patient prior to entering in a clinical study. Consent must be documented by obtaining the dated signature both of the patient and of the person conducting the consent discussion on the consent form. If local law does not allow written consent, then oral consent, attested to by the dated signature of an impartial witness (someone not involved with the conduct of the study), is the required alternative.

If the patient is illiterate, an impartial witness should be present during the entire informed consent reading and discussion. Afterward, the patient should sign and date the informed consent, if capable. The impartial witness should also sign and date the informed consent along with the individual who read and discussed the informed consent (i.e. study staff personnel).

If the patient is legally incompetent (i.e. a minor or mentally incapacitated), the written consent of a parent, legal guardian or legal representative must be obtained. Depending on local law or review committee requirements such consent may also need to be signed by an impartial witness.

The information from the consent form should be translated and communicated to the patient in language understandable to the patient. When the study patient population includes non-English speaking people, an accurately translated consent form should be provided with a written statement by the translator (whether the translator is the investigator, the Clinical Monitor, or a professional translator), indicating that the consent form is an accurate translation of the accompanying English version.

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

Patients may undergo study screening tests prior to giving written informed consent provided that these tests are considered part of standard care.

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

3.2.5.1.1 Consent for Archival Tumor Tissue

Collection of archived tumor tissue is optional but highly desirable in this study. Specimens will be analyzed to explore candidate response biomarkers, which is a strong general objective of the MK-3475 program. A patient does not need to wait to enter the study while the archival tumor specimen is being obtained. (See also Sections 1.7 and 2.1.3).

3.2.5.1.2 Consent for Tumor Biopsy

Collection of fresh biopsies of a tumor lesion before start of study therapy and approximately 2 months after start of therapy will be optional for this study. Specimens will be analyzed to explore potential differences in candidate response biomarkers between archival tumor tissue and fresh tumor biopsies, and potential changes in biomarker expression and other potentially informative tumor characteristics (e.g., amount of tumor-infiltrating lymphocytes, macrophages, etc) after 2 months on study therapy compared to pre-study (See also Sections 1.7 and 2.1.3).

3.2.5.2 Assignment of Baseline Number/Screening

After the patient has signed the consent form, the site will assign a unique screening (baseline) number. Once assigned, a baseline number cannot be reused for any reason.

After the patient has completed all baseline (screening) procedures and met all requirements of inclusion/exclusion criteria, the treating center will contact the SPONSOR to enroll the patient and provide the required eligibility information (refer to Sections 2.2 and 2.3). The center will complete a Patient Registration Form (refer to Administrative Binder) and fax it to the SPONSOR prior to enrolling the patient.

3.2.5.3 Registration/Allocation

Patients who meet the inclusion/exclusion criteria are eligible to enter into the study.

The SPONSOR will assign an Allocation Number (AN) to the patient and return (fax) this information to the center. The AN is a unique number; once assigned, it becomes the permanent study identifier for that patient when they receive their first infusion of MK-3475. In the event a patient is enrolled on the study but does not begin treatment, that patient's allocation number will not be reassigned. Patients who do not meet entry criteria will not be assigned an allocation number.

The center must account for all patients screened and enrolled. A patient participation log is to be completed with the patient's baseline number, allocation number (if patient is

enrolled), date of consent, and date of the initial administration of study drug. If a patient is not enrolled, the reason for exclusion from the study will be documented on this log.

Treatment will begin within 7 days from the date of registration.

A note referring to inclusion in the study will be documented in the patient medical records along with the allocation number and date of consent. The SPONSOR or SPONSOR's representative will keep the investigators informed of the screening activities, enrollment, and dose group availability.

Patients enrolled in one dose group cannot be re-enrolled in another dose group.

All patients will be given information identifying them as a participant in a research protocol. The information will identify appropriate contact and corresponding telephone number to be utilized in the event of an emergency.

A single patient/subject cannot be assigned more than 1 allocation number.

3.2.5.4 Treatment/Evaluation/Follow-Up

3.2.5.4.1 Study Visits

Procedures should be performed as close to the scheduled time as possible. The exact time at which a procedure is performed must be recorded in the patients study records or appropriate worksheet (if applicable). Any nonscheduled procedures required for urgent evaluation of safety concerns take precedence over all routine scheduled procedures.

A detailed outline of all scheduled study procedures is provided in the Study Flow Chart (Section 1.7). Procedures should be performed at the study center where the patient is being treated.

Blood collections for safety evaluation assume priority over other procedures. Whenever possible, blood samples should be obtained by fresh peripheral venipuncture. If a patient does not have peripheral access, the sample may be collected from a central catheter immediately after an initial withdrawal of at least 10 mL of blood; or preferably, after a series of other blood sample collections from the central catheter.

Pharmacokinetic blood sampling will assume priority after blood sampling for safety evaluation. The exact days and times at which PK sampling are performed must be recorded on the CRF.

The patient will be assessed for adverse experiences per the Study Flow Chart (Section 1.7) and at all unscheduled visits.

3.2.5.4.2 Vital Signs

To the extent feasible, blood pressure will be taken on the same arm throughout the study. A large cuff should be used for obese patients. Patients must be resting in a sitting position for 10 minutes prior to obtaining vital signs. If blood pressure is >150/100 in a

patient without a history of hypertension, or increased >20 mmHg (diastolic) from baseline measurement in a patient with a previous history of hypertension, the assessment should be repeated in 10 minutes for confirmation.

3.2.5.4.3 Medical History

The investigator will obtain the patient's medical history at the Pre-Study visit. 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.

3.2.5.4.4 Physical Examination

A complete physical examination will be performed at the Pre-Study visit. A physical examination with directed evaluation as judged appropriate by the Investigator will be performed as per the flow chart.

3.2.5.4.5 Electrocardiogram (ECG)

A 12-lead ECG should be performed at Screening, at the End of Study visit, and during study at the timepoints described in Section 1.7.

3.2.5.4.6 Guidelines for Study Drug Administration

MK-3475 will be administered as a 30 minute IV infusion. In Part A, 3 dose levels of MK-3475 will be evaluated: 1 mg/kg, 3 mg/kg and 10 mg/kg. To ascertain proper PK sampling and analysis, the interval between the first and second dose in Part A will be 28 days. In subsequent cycles, the dosing interval will be 14 days. Patients in Part B will receive the preliminary MTD identified in Part A at a dosing interval of 14 days.

The specific time of study drug 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.

Specific instructions for dose calculation, reconstitution, preparation of the infusion fluid, and administration of MK-3475 are provided in the Procedures Manual.

3.2.5.4.7 Rules for Dose Escalation and Confirmation

DLTs observed in Cycle 1 will be used to determine escalation to the next dose level. The study is using a modified 3+3 design based on the so-called TPI method [18] and has 2 parts: a dose escalation part (Part A), and Part B (which includes the dose confirmation part according to the TPI method). The guidelines used for dose escalation and dose confirmation are shown in Table 3-1.

Table 3-1

Dose Escalation and Dose Confirmation Guidelines

		Number of patients treated at current dose level											
		3	4	5	6	7	8	9	10	11	12	13	14
Number of DLTs	0	E	E	E	E	E	E	E	E	E	E	E	E
	1	S	S	S	E	E	E	E	E	E	E	E	E
	2	DU	D	D	D	S	S	S	S	E	E	E	E
	3	DU	DU	DU	DU	D	D	D	D	S	S	S	S
	4		DU	DU	DU	DU	DU	DU	D	D	D	D	D
	5			DU	DU	DU	DU	DU	DU	DU	DU	DU	D
	6				DU	DU	DU	DU	DU	DU	DU	DU	DU
	7					DU	DU	DU	DU	DU	DU	DU	DU

DLT = Dose-Limiting Toxicities (for definition of DLTs, see Section 2.4.2)
E = Escalate to the next higher dose
S = Stay at the current dose
D = De-escalate to the next lower dose
DU = The current dose is unacceptably toxic; do not re-escalate to this dose

The rules applied in the dose escalation part are as follows:

- An initial cohort of 3 patients is enrolled.
- If 0/3 patients develops a DLT, escalation to the next dose will occur.
- If 1/3 patients develops a DLT:
    - Another 3 patients will be enrolled at this dose level.
        - If 0 of the 3 new patients develops a DLT (for a total of 1/6 patients with a DLT at this dose level), escalation to the next dose level will occur.
        - If 1 of the 3 new patients develops a DLT (for a total of 2/6 patients with a DLT at this dose level), the dose escalation stage of the trial will be terminated, the current dose will be considered the preliminary MTD, and the study will proceed to the dose confirmation stage.
        - If >1 of the 3 new patients develop a DLT (for a total of >2/6 patients with a DLT at this dose level), the dose escalation stage of the trial will be terminated, the dose directly below the current dose will be considered the preliminary MTD, and the study will proceed to the confirmation stage of that dose.
- If ≥2/3 patients develop a DLT, the dose escalation stage of the trial will be terminated, the dose directly below the current dose will be considered the preliminary MTD, and the study will proceed to the confirmation stage of that dose.

It is conceptually acceptable to de-escalate to an intermediate, not pre-defined and not previously-studied dose, if evaluation of toxicity at such a dose is desired in lieu of proceeding directly to the dose confirmation stage of the study. If this approach is taken, 3 new patients should be enrolled at the new intermediate dose, and the aforementioned rules should be used to determine further enrollment at this dose level.

If the highest candidate dose of 10 mg/kg is studied during dose escalation, and 0/3 patients or ≤1/6 patients develop a DLT at that dose, then dose escalation will terminate with this finding and 10 mg/kg is considered the preliminary MTD.

In the dose escalation part, the study will enroll patients with MEL or any carcinoma type, and patients may have non-measurable disease.

Dose Confirmation Part

The objective of dose confirmation is to refine the estimate of the MTD. Dose confirmation involves the expansion of at least 1 dose studied in the dose escalation stage of the study.

Dose confirmation will begin with expansion of the preliminary MTD identified in the dose escalation stage described above. The dose confirmation part will continue until ≤3 of 14 patients (combined from Part A and Part B) experience a DLT or until a total of 14 patients within the 2 disease-specific cohorts have been enrolled (with 7 patients each for MEL and RCC), whichever comes first. As patients become evaluable for DLT assessment, the number of patients who are evaluable for DLT versus the number of patients who developed a DLT will be continuously assessed and de-escalation and re-escalation to eligible doses will occur as shown in Table 3-1.

Patients may be enrolled continuously (i.e., without waiting for Cycle 1 completion of patients who have received the first dose) unless a DLT is observed at the particular dose. Once a DLT is observed, the number of patients who are enrolled at that dose but are not yet fully evaluable for DLT assessment may not exceed the number of remaining patients who are at risk of developing a DLT before the dose would be considered unacceptably toxic (denoted as DU in Table 3-1). For example, if 1/7 patients have experienced a DLT at a given dose level, no more than an additional 4 patients should be enrolled at this dose level until additional DLT data are available. This is because this dose level would be considered unacceptably toxic if all 4 of the additional patients experience a DLT (i.e., 5/11 patients with DLT in Table 3-1).

If enrollment expands to 14 patients for a dose level, ≤3 of the 14 patients develop a DLT and <14 patients with MEL and RCC have been enrolled who have measurable disease, then accrual will continue at that dose until 14 such patients will be enrolled (specifically, 7 patients each with MEL and RCC, respectively). If enrollment expands to 14 patients for a dose level and >3/14 patients develop a DLT, then the next lower dose may be expanded to further explore the dose-response relationship. Note that while 20% has

been the target toxicity rate used to generate the guidelines in Table 3-1, the observed rate of patients with DLT at the MTD may be slightly above or below 20%.

For preliminary evaluation of anti-tumor activity in MEL and RCC, Part B will enroll up to 7 patients each with MEL and RCC who have measurable disease. The definitive number of such patients to be enrolled in the confirmation part will depend on how many patients with MEL and RCC and measurable disease had been enrolled during the escalation part.

3.2.5.4.8 Guidelines for Dose Modifications

Dose reduction or dose increase of MK-3475 will not be permitted in individual patients.

In patients who have a DLT-type AE (see Section 2.4.2 for definition) or a Grade 2 non-dermatologic immune-related AE, study therapy will be held until resolution of toxicity to grade 0-1. In the event of insufficient resolution of toxicity 4 weeks after administration of study drug, study therapy will be discontinued. In patients who continue on study therapy after experiencing such toxicity, the dosing interval in subsequent cycles will be increased to 3 weeks. Only 1 dosing delay due to toxicity will be permitted. In the event of a second occurrence of a toxicity which would require dosing delay, study therapy will be discontinued.

The same dose delay guidelines apply to patients who experience an AE which is not equivalent to a DLT-type AE but requires dose delay in the opinion of the Investigator in order to ensure appropriate safety of a study patient.

In patients who experience an infusion reaction (i.e., an anaphylactoid reaction), the following guidelines should be followed:

- Grade 1 or 2: Reduce the infusion rate by 50% for the entire remaining duration of that infusion. In the next cycle, the infusion rate should be extended to 1 hour, patients should receive oral premedication with an antihistamine (e.g., diphenhydramine or equivalent) and an anti-pyretic (e.g., paracetamol or equivalent), and they should be closely monitored for clinical signs and symptoms of an infusion reaction.
- Grade 3 or 4: Immediately stop the infusion. Patients who experience a Grade 3 or 4 infusion reaction should be discontinued from further study therapy.
- When an infusion reaction occurs, proper medical management should be instituted immediately as per type of clinical signs and symptoms and the severity of the reaction (e.g., oral or IV glucocorticoids, epinephrine, bronchodilators, oxygen).

3.2.5.4.9 Treatment Holidays

If requested by a patient and considered appropriate and in the best interest of the patient by the Investigator, patients who have been on study therapy for >6 months may have 1 treatment holiday of up to 4 weeks in continuous duration (i.e., skip 1 dose) in each of the

three 6-months periods (i.e., 7-12 months; 13-18 months; 19-24 months) over the maximum study time of 2 years (i.e., patients may have a maximum of 3 treatment holidays if they are on study for the full duration of 2 years).

3.2.5.4.10 Supportive Care Guidelines

Patients will be permitted to receive appropriate supportive care measures as deemed necessary by the treating Investigator including but not limited to the items outlined below:

- **Diarrhea**: Diarrhea should be treated promptly with appropriate supportive care, including administration of an anti-diarrheal agent according to standard practice guidelines. Anti-diarrheal agents should not be taken prophylactically. Patients should be instructed to begin taking anti-diarrheal medication at the first sign of: 1) poorly formed or loose stool, 2) occurrence of more bowel movements than usual in 1 day or 3) unusually high volume of stool. Anti-diarrheal agents should be deferred if blood or mucus is present in the stool or if diarrhea is accompanied by fever. In this setting, appropriate diagnostic microbiologic specimens should be obtained to exclude an infectious etiology. Patients should also be advised to drink liberal quantities of clear fluids to help prevent dehydration.
- **Nausea/vomiting**: Nausea and vomiting should be treated aggressively, and consideration should be given in subsequent cycles to the administration of prophylactic antiemetic therapy according to standard institutional practice. Patients should be strongly encouraged to maintain liberal oral fluid intake.
- **Anemia**: Transfusions and/or erythropoietin may be utilized as clinically indicated for the treatment of anemia, but should be clearly noted as concurrent medications.
- **Neutropenia**: Prophylactic use of colony-stimulating factors including Granulocyte Colony-Stimulating Factor (G-CSF), pegylated G-CSF or Granulocyte Macrophage Colony-Stimulating Factor GM-CSF is not allowed in this study. Therapeutic use of G-CSF is allowed in patients with febrile Grade 4 neutropenia or Grade 4 neutropenia lasting >7 days, according to standard institutional practice.
- **Thrombocytopenia**: Transfusion of platelets may be used if clinically indicated.
- **Anti-infectives**: Patients with a documented infectious complication should receive oral or IV antibiotics or other anti-infective agents as considered appropriate by the treating Investigator for a given infectious condition, according to standard institutional practice.
- **Immune-related adverse events**: Patients who develop an irAE (e.g., colitis, skin rash, uveitis, hypo- or hyperthyroidism, hypophysitis, or any other), should be discussed immediately with the SPONSOR. Depending on the type and severity of an irAE, oral or intravenous treatment with a corticosteroid should be considered, in addition to appropriate symptomatic treatment of a given condition.
- **Infusion reaction**: Patients should be closely monitored for an infusion reaction during and immediately following drug infusion. In patients who experience an

anaphylactoid-type reaction during or immediately following an infusion, proper medical management should be instituted immediately as per type of clinical signs and symptoms and the severity of the reaction. This includes, but is not limited to, oral or IV glucocorticoids, epinephrine, bronchodilators, and oxygen.

- If the reaction occurs during an infusion, the infusion should be stopped immediately in the event of Grade 3 or 4 reactions. Patients with Grade 3 or 4 infusion reactions will be discontinued from study therapy. In the event of Grade 1 or 2 reactions, the infusion rate should be reduced by 50% for the entire remaining duration of that infusion. (See also Section 3.2.5.4.8)

3.2.5.4.11 Duration of Therapy

Treatment with MK-3475 on this study may continue until one of the following events occurs:

- Documented disease progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse experiences
- Need for >1 dose delay due to toxicity as per the dose delay guidelines described in Section 3.2.5.4.8
- Patient withdraws consent
- If in the opinion of the Investigator, a change of therapy would be in the best interest of the patient
- Patient is lost to follow-up
- Pregnancy in patient
- Patient reaches 24 months of treatment (measured from start of study treatment).
  - Patients may continue on study therapy beyond 2 years if the Investigator considers this to be in the best interest of the patient based on an assessment of clinical benefit and potential risks. Continuation of study therapy beyond 2 years has to be explicitly approved by the SPONSOR, and will be contingent on the continued availability of MK-3475 drug product. Efficacy and safety monitoring of these patients, including all laboratory analyses, will follow the guidelines for Cycle 2 and Additional Cycles as described in Section 1.7, Study Flow Chart.

If a patient withdraws from the study, the procedures will be followed as described in Section 3.2.3.4.12.

3.2.5.4.12 Discontinuation Visit

At the time the patient is discontinued from treatment, the End of Study Visit procedures and assessment should be performed as listed in the Study Flow Chart (Section 1.7). The patient will be monitored for adverse events up to 30 days after discontinuation from the study or resolution of toxicity to Grade 0-1, whichever occurs later. Patients who start another cancer therapy before the planned End of Study Visit at approximately 30 days after last administration of study drug will be no longer monitored for adverse events in this study. The discontinuation visit should occur prior to the patient receiving any non-study cancer therapy.

3.2.5.4.13 Duration of Follow-up

All patients have to be followed for at least 30 days after their last dose of study drug or until initiation of a new anti-cancer treatment, whichever occurs first.

Patients who are discontinued from the study due to an unacceptable drug related adverse event will be followed until the resolution of the AE to Grade 0-1 or stabilization or until beginning of a new therapy for their cancer, whichever occurs first.

In patients who discontinue before 24 months of study therapy and have no documented disease progression, every effort should be made to follow the patient (1) for approximately 6 months without disease progression, (2) until start of a new anti-cancer treatment, (3) until documented disease progression, or (4) until death, whichever occurs first. The interval of imaging studies should follow the guidelines as the Study Flow Chart (Section 1.7; footnote 22).

The end of the study is designated as the time point when all patients have discontinued the study or are a minimum of 6 months post initial study medication administration, whichever occurs first. However, patients may continue on study therapy and all study procedures and guidelines as described in the study protocol will continue to apply, including full documentation and capture of all applicable patient and study data.

3.2.5.5 Discontinuation/Withdrawal from Study

Subjects/patients may withdraw at any time or be dropped from the study at the discretion of the investigator should any untoward effects occur. In addition, a subject/patient may be withdrawn by the investigator or the SPONSOR if he/she violates the study plan or for administrative and/or other safety reasons. The investigator or study coordinator must notify the SPONSOR immediately when a subject/patient has been discontinued/withdrawn due to an adverse experience (telephone or FAX). When a subject/ patient discontinues/withdraws prior to study completion, all applicable activities scheduled for the final study visit should be performed at the time of discontinuation. Any adverse experiences which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in section 3.4 SAFETY MEASUREMENTS - DETAILS.

Subjects/patients who discontinue from the study for reasons unrelated to the study (e.g., personal reasons) will be replaced as required for the study to meet its objectives. The decision to remove a subject/patient and to replace dropouts will be made jointly by the investigator, SPONSOR Clinical Monitor, and SPONSOR study statistician. The replacement will generally receive the same treatment or treatment sequence (as appropriate) as the allocation number replaced. Both the replacement and originally allocated number will be unique numbers.

3.3 EFFICACY/PHARMACOKINETIC/IMMUNOGENICITY, ETC. MEASUREMENTS

3.3.1 Efficacy Measurements

All baseline efficacy evaluations should be performed as close as possible to the beginning of treatment. Baseline imaging must be performed no more than 30 days before enrollment. The same imaging method should be used to characterize each identified and reported lesion at baseline and during follow-up.

Tumor status will be compared to baseline and response will be evaluated by physical examination, anatomic imaging measurement, serum tumor markers (where appropriate), and performance status.

3.3.1.1 Radiographic Assessment

The baseline tumor imaging (CT or MRI, with a preference for CT) examinations must be performed within 30 days before enrollment. Patients continuing on study will have follow-up imaging performed approximately every 2 months in the first 12 months and approximately every 3 months in the second year. The same imaging technique should be used in a patient throughout the study. After first documentation of response (complete response or partial response), imaging performed at the next regularly scheduled time point (e.g., 2 months later in the first 12 months of study therapy) will be used for response confirmation.

3.3.1.2 Response Criteria

Overall tumor response and progression will be evaluated at the designated time points according to RECIST 1.1 as described in the Investigator's Imaging Operations Manual (IIOM). In addition, exploratory evaluation of volumetric tumor response will be performed by a central imaging vendor (see IIOM for details).

3.3.1.3 Pharmacokinetic Measurements

Procedures describing serum sample collection, processing, storage, and shipping details are provided in the Procedures Manual.

The time points for PK blood sampling are described in Section 1.7 (Study Flow Chart: Details of Sampling for Pharmacokinetics and Pharmacodynamics).

3.3.1.4 Pharmacodynamic Measurements

Procedures describing sample collection, processing, storage, and shipping details are provided in the Procedures Manual. The time points for PD blood sampling are described in Section 1.7 (Study Flow Chart: Details of Sampling for Pharmacokinetics and Pharmacodynamics).

3.3.1.5 Safety Monitoring

During the escalation phase of the study, the safety data of each cohort will be reviewed prior to the start of the next cohort. In addition, throughout the study the SPONSOR and Investigators will review the adverse event data on a regular basis.

3.4 SAFETY MEASUREMENTS

3.4.1 Clinical and Laboratory Measurements for Safety

Vital signs, weight, physical examinations, ECOG performance status, ECGs and laboratory safety tests (e.g., PT/aPTT, urinalysis, CBC, serum chemistries, auto-antibodies, thyroid function, viral antigen reactions, cytokine / chemokine panels) will be obtained and assessed at designated intervals throughout the study (see Study Flow Chart, Section 1.7).

Adverse events will be graded and recorded throughout the study according to NCI-CTCAE, version 4.0. Characterization of toxicities will include severity, duration, and time to onset. Safety endpoints will include all types of adverse events, in addition to laboratory safety assessments, ECOG performance scale status, ECGs, and vital signs.

3.4.2 Recording Adverse Experiences

An adverse experience is defined as any unfavorable and unintended change in the structure, function, or chemistry of the body temporally associated with the use of the SPONSOR's product, whether or not considered related to the use of the product. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition which is temporally associated with the use of the SPONSOR's product, is also an adverse experience.

Changes resulting from normal growth and development which do not vary significantly in frequency or severity from expected levels are not to be considered adverse experiences. 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.

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

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

Such events will be recorded at each examination on the Adverse Experience Case Report Forms/Worksheets.

3.4.3 Definition of an Overdose for This Protocol

Overdose is defined as:

The patient has taken (accidentally or intentionally) a dose exceeding the dose prescribed in the protocol by 20%.

3.4.3.1 Reporting of Overdose to SPONSOR

If an adverse experience(s) is associated with ("results from") the overdose of test drug or vaccine, the adverse experience(s) is reported as a serious adverse experience, even if no other criteria for serious are met.

If a dose of test drug 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 experience must be reported within 24 hours to one of the individuals listed on the sponsor contact information page found in the Administrative Binder.

3.4.4 Reporting of Pregnancy to SPONSOR

Although not considered an adverse experience, it is the responsibility of investigators or their designees to report any pregnancy in a subject/patient or a male patient's partner (spontaneously reported to them) which occurs during the study or within 30 days of completing the study. All subjects/patients who become pregnant must be followed to the completion/termination of the pregnancy. If the pregnancy continues to term, the outcome (health of infant) must also be reported to one of the individuals listed on the SPONSOR Contact Information page found in the Administrative Binder.

3.4.5 Immediate Reporting of Adverse Experiences to the SPONSOR

Any serious adverse experience should be recorded and reported within 24 hours or, at least, on the following working day to Global Pharmacovigilance via facsimile (found in the administrative binder) using the following fax number:

Fax: 908-740-2169

3.4.5.1 Serious Adverse Experiences

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

Any serious adverse experience, including death due to any cause, which occurs to any subject/patient entered into this study or within 30 days following cessation of treatment or within the established off therapy follow-up period for safety described in the protocol, whether or not related to the investigational product, must be reported within 24 hours to one of the individual(s) listed on the contact information page.

Additionally, any serious adverse experience considered by an investigator who is a qualified physician to be possibly, probably, or definitely related to the investigational product that is brought to the attention of the investigator at any time outside of the time period specified in the previous paragraph also must be reported immediately to one of the individuals listed on the sponsor contact information page found in the administrative binder.

All subjects/patients with serious adverse experiences must be followed up for outcome.

3.4.6 Evaluating Adverse Experiences

An Investigator, who is a qualified physician, will evaluate all adverse experiences according to the NCI CTCAE, version 4.0. Any adverse experiences which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the adverse experience case report form.

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

Refer to Table 3-2 for instructions in evaluating adverse experiences.

Table 3-2

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

V 4.0 CTCAE Grading	**Grade 1**	**Mild; asymptomatic or mild 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 of hospitalization indicated; disabling; limiting self care ADL.**
	Grade 4	**Life threatening consequences; urgent intervention indicated.**
	Grade 5	**Death related to AE.**
	†Results in death; or	
	†Is life threatening; or places the subject/patient, in the view of the investigator, at immediate risk of death from the experience as it occurred [Note: This does not include an adverse experience that, had it occurred in a more severe form, might have caused death.]; or	
	†Results in a persistent or significant disability/incapacity (substantial disruption of one's ability to conduct normal life functions); or	
	†**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization [including hospitalization for an elective procedure] for a preexisting condition which has not worsened does not constitute a serious adverse experience.); or	
	†**Is a congenital anomaly/birth defect** (in offspring of subject/patient taking the product regardless of time to diagnosis); or	
	Is a new cancer; (that is a condition of the study) or	
	Is an overdose (Whether accidental or intentional.) Any overdose whether or not associated with an adverse experience 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 experience when, based upon appropriate medical judgment, the event may jeopardize the subject/patient 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 experience. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the adverse experience cause the test drug to be discontinued?	
Relationship to test drug	Did the test drug cause the adverse experience? The determination of the likelihood that the test drug caused the adverse experience 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 experience based upon the available information. **The following components are to be used to assess the relationship between the test drug and the AE;** the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the test drug caused the adverse experience (AE):	
	Exposure	Is there evidence that the subject/patient was actually exposed to the test drug 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 test drug? Is the time of onset of the AE compatible with a drug-induced effect?
	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 test drug (continued)	**The following components are to be used to assess the relationship between the test drug and the AE: (continued)**	
	Dechallenge	Was the dose of test drug discontinued or 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 test drug; or (3) the study is a single-dose drug study.)
	Rechallenge	Was the subject/patient reexposed to the test drug 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 study is a single-dose drug study.) NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY THE TEST DRUG, OR IF REEXPOSURE TO THE TEST DRUG POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE SUBJECT/PATIENT, THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE U.S. CLINICAL MONITOR AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL.
	Consistency with Study Drug Profile	Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the test drug 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 drug relationship).**
Yes, there is a reasonable possibility of drug relationship.		There is evidence of exposure to the test drug. The temporal sequence of the AE onset relative to the administration of the test drug is reasonable. The AE is more likely explained by the test drug than by another cause. **Depending on data collection method employed, drug relationship may be further graded as follows:**
	Definitely related	There is evidence of exposure to the test drug. The temporal sequence of the AE onset relative to administration of the test drug is reasonable. The AE is more likely explained by the test drug than by another cause. Dechallenge is positive. Rechallenge (if feasible) is positive. The AE shows a pattern consistent with previous knowledge of the test drug or test drug class.
	Probably related	There is evidence of exposure to the test drug. The temporal sequence of the AE onset relative to administration of the test drug is reasonable. The AE is more likely explained by the test drug than by another cause. Dechallenge (if performed) is positive.
	Possibly related	There is evidence of exposure to the test drug. The temporal sequence of the AE onset relative to administration of the test drug is reasonable. The AE could have been due to another equally likely cause. Dechallenge (if performed) is positive.
No, there is not a reasonable possibility of drug relationship		Subject did not receive the test drug OR temporal sequence of the AE onset relative to administration of the test drug is not reasonable OR there is another obvious cause of the AE. (Also entered for a subject with overdose without an associated AE.) **Depending on data collection method employed, drug relationship may be further graded as follows:**
	Probably not related	There is evidence of exposure to the test drug. There is another more likely cause of the AE. Dechallenge (if performed) is negative or ambiguous. Rechallenge (if performed) is negative or ambiguous.
	Definitely not related	The subject/patient did not receive the test drug. OR Temporal sequence of the AE onset relative to administration of the test drug is not reasonable. OR There is another obvious cause of the AE.

3.4.7 SPONSOR Responsibility for Reporting Adverse Experiences

All adverse experiences will be reported to regulatory agencies, IRB/IECs, and investigators in accordance with all applicable global laws and regulations.

3.5 STATISTICAL ANALYSIS PLAN (SAP)

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, changes are made to primary, secondary or tertiary objectives and/or hypotheses, or to the statistical methods related to those objectives and/or hypotheses, then those changes, along with an explanation as to when and why they occurred, will be listed in the Clinical Study Report (CSR) for the study. Post hoc exploratory analyses will be clearly identified in the CSR. No separate Statistical Analysis Plan (SAP) will be issued for this study.

3.5.1 Responsibility for Analyses/In-House Blinding

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

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

3.5.2 Hypotheses/Estimation

Objectives and hypotheses of the study are stated in Section 2.1.

3.5.3 Analysis Endpoints

3.5.3.1 Efficacy Endpoints

Although disease response is not a primary endpoint of the study, it will be assessed during the study by diagnostic anatomic imaging (CT or MRI), clinical (physical examination) evaluations, and laboratory (serum tumor markers) measurements if applicable. Overall tumor response and response duration will be assessed using RECIST version 1.1, as described in the IIOM.

3.5.3.2 Pharmacokinetic and Pharmacodynamic Endpoints

Blood samples for serum levels of MK-3475 and analysis of target engagement will be obtained at the time points listed in Section 1.7. Study Flow Chart.

3.5.3.3 Safety Endpoints

The primary safety endpoint is DLT. Other safety endpoints are other adverse events, laboratory safety assessments, ECOG performance status, ECGs, vital signs and physical examinations.

3.5.4 Analysis Populations

3.5.4.1 Efficacy Analysis

The efficacy analyses will be based on the population of patients with measurable disease at baseline per RECIST 1.1 criteria.

3.5.4.2 Safety Analysis

The All Patients as Treated (APaT) population will be used for the analysis of safety data in this study. The APaT population consists of all patients who received at least 1 dose of study treatment.

In order for a patient to be considered evaluable for the analysis of DLT, the patient must have either had a DLT in Cycle 1, or had received at least 90% of the prescribed dose of MK-3475 in Cycle 1 and completed all safety evaluations up to and including at least 28 days after the first administration of MK-3475 without experiencing a DLT. Should a patient without DLT not adequately complete the evaluation period associated with the first cycle of study therapy (i.e., discontinue prematurely due to a reason unrelated to study therapy), or should a patient have received <90% of a prescribed dose and had no DLT, such patients will be replaced.

3.5.5 Statistical Methods

3.5.5.1 Efficacy Analysis

Response rate and its 95% confidence interval based on binomial distribution will be provided. Response duration will be listed and descriptively summarized as appropriate.

3.5.5.2 Pharmacokinetic Analysis

MK-3475 pharmacokinetic variables (e.g., C_{max}, T_{max}, C_{trough} and AUC) will be calculated as appropriate and summary statistics will be provided. Graphical, non-compartmental and potentially exploratory compartmental analyses will be used for the analysis of the pharmacokinetic data.

3.5.5.3 Pharmacodynamic Analysis

PD-1 receptor occupancy and PD-1 target modulation will be analyzed as appropriate and summary statistics will be provided.

3.5.5.4 Safety Analysis

Safety and tolerability will be assessed by clinical review of all relevant parameters including DLTs, other AEs, laboratory tests, ECG measurements, and vital signs.

DLTs will be listed. At the end of the trial, a dose-response relationship for the rate of experiencing a DLT in Cycle 1 will be estimated using the pooling-of-adjacent-violators algorithm. This dose-response estimation will be used to support determination of the

MTD. The dose-response relationship, overall tolerability and safety profile, and the PK and PD data will inform the determination of a recommended Phase 2 dose.

The 80% confidence intervals for DLT and drug-related toxicity rates in Cycle 1 for the identified MTD level will be provided. Summary statistics (median and range) for time to onset of first drug-related toxicity in each dose level will be provided. Adverse experiences will be summarized as counts and frequencies for each dose level. Laboratory assessments, vital signs, and other safety endpoints will be summarized as appropriate.

3.5.6 Multiplicity

No formal statistical hypothesis is being tested in this study. Therefore, no multiplicity adjustment needs to be considered.

3.5.7 Sample Size and Power Calculations

The primary objective of the study is to determine the safety and tolerability of MK-3475. A modified 3+3 design based on the so-called TPI method [18] will be used to estimate the MTD (see Section 3.2.5.4.7 for details). The sample size of the study depends primarily on clinical considerations rather than on statistical considerations. Specifically, the final number of subjects enrolled in the study will depend on empirical safety (DLT) observations and how many patients with MEL and RCC and measurable disease are enrolled during Part A of the study. With 14 patients at a dose, the upper bound of the 80% confidence interval for DLT rate excludes a rate of 33% if 2 or fewer patients develop a DLT. Table 3-3 shows the 80% confidence intervals for various numbers of DLT in 14 patients.

Table 3-3

Confidence Intervals for DLT Rate

Number of Patients	Number of DLTs	DLT Rate	80% Confidence Interval
14	0	0.0%	(0.0%, 15.2%)
14	1	7.1%	(0.7%, 25.1%)
14	2	14.3%	(3.9%, 33.7%)
14	3	21.4%	(8.1%, 41.7%)

The study plans to enroll 7 patients each with MEL and RCC who have measurable disease and are evaluable for response assessment per RECIST criteria. Seven patients provide a power of 79% to rule out a true response rate of 20% if no patient responds.

In this Phase I study, a maximum of approximately 32 eligible patients evaluable for safety and tolerability will be enrolled, with approximately 18 patients in Part A and approximately 14 patients in Part B.

3.6 LABELING, PACKAGING, STORAGE, DISPENSING, AND RETURN OF CLINICAL SUPPLIES

3.6.1 Patient and Replacements Information

Clinical supplies will be packaged to support enrollment of approximately **32** patients/subjects. Clinical supplies will be packaged according to an allocation schedule generated by the SPONSOR**.**

3.6.2 Product Descriptions

Investigational materials will be provided by the SPONSOR as summarized in Table 3-4.

Table 3-4

Product Descriptions

Product Name & Potency	**Dosage Form**
MK-3475 (SCH900475) 50mg	Powder for injection

3.6.3 Primary Packaging and Labeling Information

Supplies will be packaged in **glass vials** as described in Table 3-5 below.

Table 3-5

Packaging of Clinical Supplies

Product Name & Potency	Fill Count	Dosing Instructions
MK-3475 (SCH900475)	50 mg/vial	Administer as directed

Container label text may include the following:

• Packaging Lot ID # • Fill Count & Dosage Form	• Dosing Instructions • Storage Conditions • Compound ID - Protocol # • Country regulatory requirements • SPONSOR address (If applicable)

3.6.4 Secondary Packaging and Labeling Information (kit)

Supplies will be packaged **in kit boxes containing 1 vial.** Kit configuration is subject to change as a result of packaging constraints.

Label text may include the following:

• Packaging Lot ID # • Fill Count & Dosage Form	• Dosing Instructions • Storage Conditions • Compound ID - Protocol # • Country regulatory requirements • SPONSOR address (If applicable)

3.6.5 Clinical Supplies Disclosure

This study is open-label; therefore, the patient, the investigator's site personnel and the SPONSOR are not blinded to treatment. Drug identity (name, strength) is included in the label text; disclosure envelopes are not provided.

3.6.6 Storage and Handling Requirements

Clinical supplies should be kept in a secured location at refrigerated temperature (2-8ºC). The clinical supplies storage area at the site must be monitored by the site staff for temperature consistency with the acceptable storage temperature range specified in this protocol or in the product label attached to the protocol. Documentation of temperature monitoring should be maintained.

3.6.7 Standard Policies / Return of Clinical Supplies

Investigational clinical supplies must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated personnel have access. Clinical supplies are to be dispensed only in accordance with the protocol. The investigator is responsible for keeping accurate records of the clinical supplies received from the SPONSOR, the amount dispensed to and returned by the subjects/patients, and the amount remaining at the conclusion of the study. In accordance with Good Pharmacy Practices, gloves should always be worn by study personnel if directly handling tablets or capsules that are returned (i.e., when counting returns). The Clinical Monitor should be contacted with any questions concerning investigational products where special or protective handling is indicated. At the end of the study, all clinical supplies including partial and empty containers must be returned as indicated on the Contact Information page(s).

3.7 DATA MANAGEMENT

Information regarding Data Management procedures for this protocol will be provided by the SPONSOR.

3.8 BIOLOGICAL SPECIMENS

Information regarding biological specimens for this protocol will be provided by the SPONSOR.

Product: MK-3475 1
Protocol/Amendment No.: 001-00

4. ADMINISTRATIVE AND REGULATORY DETAILS

4.1 CONFIDENTIALITY

4.1.1 Confidentiality of Data

For Studies Conducted Under the U.S. IND

Particular attention is drawn to the regulations promulgated by the Food and Drug Administration under the Freedom of Information Act providing, in part, that information furnished to clinical investigators and Institutional Review Boards will be kept confidential by the Food and Drug Administration only if maintained in confidence by the clinical investigator and Institutional Review Board.

For All Studies

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, 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 study 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.

4.1.2 Confidentiality of Subject/Patient Records

For All Studies

By signing this protocol, the investigator agrees that the SPONSOR (or SPONSOR representative), Institutional Review Board/Independent Ethics Committee (IRB/IEC), or Regulatory Agency representatives may consult and/or copy study documents in order to verify worksheet/case report form data. By signing the consent form, the subject/patient agrees to this process. If study documents will be photocopied during the process of verifying worksheet/case report form information, the subject/patient will be identified by unique code only; full names/initials will be masked prior to transmission to the SPONSOR.

For Studies Conducted Under the U.S. IND

By signing this protocol, the investigator agrees to treat all patient data used and disclosed in connection with this study in accordance with all applicable privacy laws, rules and regulations, including all applicable provisions of the Health Insurance Portability and Accountability Act and its implementing regulations, as amended from time to time. ("HIPAA").

4.1.3 Confidentiality of Investigator Information

For All Studies

By signing this protocol, the investigator recognizes that certain personal identifying information with respect to the investigator, and all subinvestigators and study site

personnel, may be used and disclosed for study management purposes, as part of a regulatory submissions, and as required by law. This information may include:

- name, address, telephone number, and email address;
- hospital or clinic address and telephone number;
- curriculum vitae or other summary of qualifications and credentials; and
- 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 agencies or to other investigators. By signing this protocol, the investigator expressly consents to these uses and disclosures.

For Multicenter Studies
In order to facilitate contact between investigators, the SPONSOR may share an investigator's name and contact information with other participating investigators upon request.

4.2 COMPLIANCE WITH LAW, AUDIT, AND DEBARMENT

By signing this protocol, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol; 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 study.

The Code of Conduct, a collection of goals and considerations that govern the ethical and scientific conduct of clinical investigations sponsored by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., is attached.

The investigator also agrees to allow monitoring, audits, Institutional Review Board/Independent Ethics Committee review, and regulatory agency inspection of trial-related documents and procedures and provide for direct access to all study-related source data and documents.

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

The Investigator shall prepare and maintain complete and accurate study documentation in compliance with Good Clinical Practice standards and applicable federal, state, and local laws, rules and regulations; and, for each subject/patient participating in the study,

provide all data, and upon completion or termination of the clinical study submit any other reports to the SPONSOR as required by this protocol or as otherwise required pursuant to any agreement with the SPONSOR.

Study documentation will be promptly and fully disclosed to the SPONSOR by the investigator upon request and also shall be made available at the investigator's site upon request for inspection, copying, review, and audit at reasonable times by representatives of the SPONSOR or any regulatory agencies. 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 study documentation and worksheets/case report forms.

International Conference of Harmonization Good Clinical Practice guidelines (Section 4.3.3) 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.

According to European legislation, a SPONSOR must designate a principal or coordinating investigator (CI) to review the report (summarizing the study results) and confirm that to the best of his/her knowledge the report accurately describes conduct and results of the study. The SPONSOR may consider one or more factors in the selection of the individual to serve as the CI (e.g., thorough understanding of clinical trial methods, appropriate enrollment of subject/patient cohort, timely achievement of study milestones, availability of the CI during the anticipated review process).

The investigator will promptly inform the SPONSOR of any regulatory agency inspection conducted for this study.

Persons debarred from conducting or working on clinical studies by any court or regulatory agency will not be allowed to conduct or work on this SPONSOR's studies. The investigator will immediately disclose in writing to the SPONSOR if any person who is involved in conducting the study 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 site's IRB/IEC.

4.3 COMPLIANCE WITH FINANCIAL DISCLOSURE REQUIREMENTS

By signing this protocol, the investigator agrees to provide to the SPONSOR accurate financial information to allow the SPONSOR to submit complete and accurate certification and disclosure statements as required by U.S. Food and Drug Administration regulations (21 CFR Part 54). The investigator further agrees to provide this information on a Financial Disclosure/Certification Form that is provided by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. This requirement also extends to subinvestigators. The investigator also consents to the transmission of this information to Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. in the United States for

these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

4.4 QUALITY CONTROL AND QUALITY ASSURANCE

By signing this protocol, the SPONSOR agrees to be responsible for implementing and maintaining quality control and quality assurance systems with written 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 study.

4.5 COMPLIANCE WITH INFORMATION PROGRAM ON CLINICAL TRIALS FOR SERIOUS OR LIFE THREATENING CONDITIONS

Under the terms of The Food and Drug Administration Modernization Act (FDAMA), the SPONSOR of the study is solely responsible for determining whether the study is subject to the requirements for submission to the Clinical Trials Data Bank, http://clinicaltrials.gov/. Merck, as SPONSOR of this study, will review this protocol and submit the information necessary to fulfill this requirement. Merck entries are not limited to FDAMA mandated trials. Merck's voluntary listings, beyond those mandated by FDAMA, will be in the same format as for treatments for serious or life-threatening illnesses. Information posted will allow patients to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate study locations and site contact information.

By signing this protocol, the investigator acknowledges that the statutory obligation under FDAMA is that of the SPONSOR and agrees not to submit any information about this study to the Clinical Trials Data Bank.

4.6 PUBLICATIONS

This study 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 study results within 12 months after the last data become available, which may take up to several months after the last patient visit in some cases such as vaccine trials. However, manuscript submission timelines may be extended on OTC studies. For studies intended for pediatric-related regulatory filings, the investigator agrees to delay publication of the study results until the SPONSOR notifies the investigator that all relevant regulatory requirements on the study drug have been fulfilled with regard to pediatric-related regulatory filings. Merck will post a synopsis of study results for approved products on www.clinicalstudyresults.org and www.clinicaltrials.gov by 12 months after the last patient's last visit or within 7 days of product approval in any major markets (United States, Europe or Japan), 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.

For multicenter studies, subsequent to the multicenter publication (or after public disclosure of the results online at www.clinicalstudyresults.org if a multicenter manuscript is not planned), an investigator and his/her colleagues may publish their data independently. In most cases, publication of individual site data does not add value to complete multicenter results, due to statistical concerns. In rare cases, publication of single site data prior to the main paper may be of value. Limitations of single 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 should meet conditions 1, 2, and 3. Significant contributions to study 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 study, final decisions on authorship and the order of authors' names will be made based on participation and actual contributions to the study and writing, as discussed above. The first author is responsible to defend 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 study 60 days prior to submission for publication/presentation. Any information identified by the SPONSOR as confidential must be deleted prior to submission. SPONSOR review can be expedited to meet publication timelines.

5. LIST OF REFERENCES

1. Disis ML. Immune Regulation of Cancer. J Clin Oncol 2010;28:4531-8.

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

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

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

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

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

7. Nomi T, Sho M, Akahori T, Hamada K, Kubo A, Kanehiro, H, et al. Clinical significance and therapeutic potential of the programmed death-1 ligand/programmed death-1 pathway in human pancreatic cancer. Clin Cancer Res 2007;13:2151-7.

8. Gao Q, Wang XY, Qiu SJ, Yamato I, Sho M, Nakajima Y, et al. Overexpression of PD-L1 significantly associates with tumor aggressiveness and postoperative recurrence in human hepatocellular carcinoma. Clin Cancer Res 2009;15: 971-9

9. Hamanishi J, Mandai M, Iwasaki M, Okazaki T, Tanaka Y, Yamaguchi K, et al. Programmed cell death 1 ligand 1 and tumor-infiltrating CD8+ T lymphocytes are prognostic factors of human ovarian cancer. Proc Natl Acad Sci USA 2007;104:3360-5.

10. Fourcade J, Kudela P, Sun Z, Shen H, Lenzner D, Guillaume P, et al. PD-1 is a regulator of NY-ESO-1-specific CD8+ T cell expansion in melanoma patients. J Immunol 2009;182:5240-9.

11. Cai G, Karni A, Oliveira EM, Weiner HL, Hafler DA, Freeman GJ. PD-1 ligands, negative regulators for activation of naive, memory, and recently activated human CD4+ T cells. Cell Immunol 2004;230:89-98

12. Blank C, Mackensen A. Contribution of the PD-L1/PD-1 pathway to T-cell exhaustion: an update on implications for chronic infections and tumor evasion. Cancer Immunol Immunother 2007;56:739-45.

13. Iwai Y, Ishida M, Tanaka Y, Okazaki T, Honjo T, Minato N. Involvement of PDL1 on tumor cells in the escape from host immune system and tumor immunotherapy by PD-L1 blockade. Proc Natl Acad Sci USA 2002;99:12293-7.

14. Tsushima, F, Tanaka, K, Otsuki, N, Youngnak, P, Iwai, H, Omura K, Azuma, M. Predominant expression of B7-H1 and its immunoregulatory roles in oral squamous cell carcinoma. Oral Oncol 2006;42:268-74.

15. Korman A, Chen B, Wang C, Wu L, Cardarelli J, Selby M. Activity of Anti-PD-1 in Murine Tumor Models: Role of "Host" PD-L1 and Synergistic Effect of Anti-PD-1 and Anti-CTLA-4. J Immunol 2007;178:abstr. 48.37.

16. Sznol M, Powderly JD, Smith DC, Brahmer JR, Drake CG, McDermott DF, et al. Safety and antitumor activity of biweekly MDX-1106 (anti-PD-1, BMS-936558/ONO-4538) in patients with advanced refractory malignancies. Proc Am Soc Clin Oncol 2010;28:abstr. 2506

17, Brahmer JR, Drake C, Wollner I, Powderly JD, Picus J, Sharfman WH, et al. Phase I study of single agent anti-programmed death-1 (MDX-1106) in refractory solid tumors: safety, clinical activity, pharmcodynamics, and immunologic correlates. J Clin Oncol 2010;28:3167-75.

18. Ji Y, Li Y, Nebiyou Bekele B. Dose-finding in phase I clinical trials based on toxicity probability intervals. Clin Trials 2007;4:235-44

19. Shirabe K, Motomura T, Muto J, Toshima T, Matono R, Mano Y, Takeishi K, Ijichi

H, Harada N, Uchiyama H, Yoshizumi T, Taketomi A, Maehara Y. Tumor-infiltrating lymphocytes and hepatocellular carcinoma: pathology and clinical management. Int J Clin Oncol. 2010 Oct 21.

20. Ruffell B, DeNardo DG, Affara NI, Coussens LM. Lymphocytes in cancer development: polarization towards pro-tumor immunity. Cytokine Growth Factor Rev.2010 Feb;21(1):3-10.

21. Bellati F, Visconti V, Napoletano C, Antonilli M, Frati L, Panici PB, Nuti M. Immunology of gynecologic neoplasms: analysis of the prognostic significance of the immune status. Curr Cancer Drug Targets. 2009 Jun;9(4):541-65.

22. Delhem N, Carpentier A, Moralès O, Miroux C, Groux H, Auriault C, Pancré V. Regulatory T-cells and hepatocellular carcinoma: implication of the regulatory T lymphocytes in the control of the immune response. Bull Cancer. 2008 Dec;95(12):1219-25.

23. Clark CE, Beatty GL, Vonderheide RH. Immunosurveillance of pancreatic adenocarcinoma: insights from genetically engineered mouse models of cancer. Cancer Lett. 2009 Jun 28;279(1):1-7.

24. Nemolato S, Fanni D, Naccarato AG, Ravarino A, Bevilacqua G, Faa G. Lymphoepitelioma-like hepatocellular carcinoma: a case report and a review of the literature. World J Gastroenterol. 2008 Aug 7;14(29):4694-6.

25. Nobili C, Degrate L, Caprotti R, Franciosi C, Leone BE, Trezzi R, Romano F, Uggeri F, Uggeri F. Prolonged survival of a patient affected by pancreatic adenocarcinoma with massive lymphocyte and dendritic cell infiltration after interleukin-2 immunotherapy. Report of a case. Tumori. 2008 May-Jun;94(3):426-30.

26. Piersma SJ, Welters MJ, van der Burg SH. Tumor-specific regulatory T cells in cancer patients. Hum Immunol. 2008 Apr-May;69(4-5):241-9.

27. Talmadge JE, Donkor M, Scholar E. Inflammatory cell infiltration of tumors: Jekyll or Hyde. Cancer Metastasis Rev. 2007 Dec;26(3-4):373-400.

28. Al-Shibli K, Al-Saad S, Andersen S, Donnem T, Bremnes RM, Busund LT. The prognostic value of intraepithelial and stromal CD3-, CD117- and CD138-positive cells in non-small cell lung carcinoma. APMIS. 2010 May;118(5):371-82.

29. Rao UN, Lee SJ, Luo W, Mihm MC Jr, Kirkwood JM. Presence of tumor-infiltrating lymphocytes and a dominant nodule within primary melanoma are prognostic factors for relapse-free survival of patients with thick (t4) primary melanoma: pathologic analysis of the e1690 and e1694 intergroup trials. Am J Clin Pathol. 2010 Apr;133(4):646-53.

30. Shen Z, Zhou S, Wang Y, Li RL, Zhong C, Liang C, Sun Y. Higher intratumoral infiltrated Foxp3+ Treg numbers and Foxp3+/CD8+ ratio are associated with adverse prognosis in resectable gastric cancer. J Cancer Res Clin Oncol. 2010 Oct;136(10):1585-95.

31. Laghi L, Bianchi P, Miranda E, Balladore E, Pacetti V, Grizzi F, Allavena P, Torri V, Repici A, Santoro A, Mantovani A, Roncalli M, Malesci A. CD3+ cells at the invasive margin of deeply invading (pT3-T4) colorectal cancer and risk of post-surgical metastasis: a longitudinal study. Lancet Oncol. 2009 Sep;10(9):877-84.

32. Li JF, Chu YW, Wang GM, Zhu TY, Rong RM, Hou J, Xu M. The prognostic value of peritumoral regulatory T cells and its correlation with intratumoral cyclooxygenase-2 expression in clear cell renal cell carcinoma. BJU Int. 2009 Feb;103(3):399-405.

33. Sasaki A, Tanaka F, Mimori K, Inoue H, Kai S, Shibata K, Ohta M, Kitano S, Mori M. Prognostic value of tumor-infiltrating FOXP3+ regulatory T cells in patients with hepatocellular carcinoma. Eur J Surg Oncol. 2008 Feb;34(2):173-9.

34. Hillen F, Baeten CI, van de Winkel A, Creytens D, van der Schaft DW, Winnepenninckx V, Griffioen AW. Leukocyte infiltration and tumor cell plasticity

are parameters of aggressiveness in primary cutaneous melanoma. Cancer Immunol Immunother. 2008 Jan;57(1):97-106.

35. Gao Q, Qiu SJ, Fan J, Zhou J, Wang XY, Xiao YS, Xu Y, Li YW, Tang ZY. Intratumoral balance of regulatory and cytotoxic T cells is associated with prognosis of hepatocellular carcinoma after resection. J Clin Oncol. 2007 Jun 20;25(18):2586-93.

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

37. Oshikiri T, Miyamoto M, Shichinohe T, Suzuoki M, Hiraoka K, Nakakubo Y, Shinohara T, Itoh T, Kondo S, Katoh H. Prognostic value of intratumoral CD8+ T lymphocyte in extrahepatic bile duct carcinoma as essential immune response. J Surg Oncol. 2003 Dec;84(4):224-8.

38. Diederichsen AC, Hjelmborg JB, Christensen PB, Zeuthen J, Fenger C. Prognostic value of the CD4+/CD8+ ratio of tumour infiltrating lymphocytes in colorectal cancer and HLA-DR expression on tumour cells. Cancer Immunol Immunother. 2003 Jul;52(7):423-8.

39. Usubütün A, Ayhan A, Uygur MC, Ozen H, Toklu C, Ruacan S. Prognostic factors in renal cell carcinoma. J Exp Clin Cancer Res. 1998 Mar;17(1):77-81.

40. Diez M, Pollán M, Enriquez JM, Dominguez P, Santana A, Tobaruela E, Mugüerza JM, Arrieta F, Rodriguez A, Ruiz A. Histopathologic prognostic score in colorectal adenocarcinomas. Anticancer Res. 1998 Jan-Feb;18(1B):689-94.

41. Ropponen KM, Eskelinen MJ, Lipponen PK, Alhava E, Kosma VM. Prognostic value of tumour-infiltrating lymphocytes (TILs) in colorectal cancer. J Pathol. 1997 Jul;182(3):318-24.

42. Shirabe K, Motomura T, Muto J, Toshima T, Matono R, Mano Y, Takeishi K, Ijichi H, Harada N, Uchiyama H, Yoshizumi T, Taketomi A, Maehara Y. Tumor-infiltrating lymphocytes and hepatocellular carcinoma: pathology and clinical management. Int J Clin Oncol. 2010 Oct 21. 963618.

43. Hiraoka N. Tumor-infiltrating lymphocytes and hepatocellular carcinoma: molecular biology. Int J Clin Oncol. 2010 Oct 6.

44. Liotta F, Gacci M, Frosali F, Querci V, Vittori G, Lapini A, Santarlasci V, Serni S, Cosmi L, Maggi L, Angeli R, Mazzinghi B, Romagnani P, Maggi E, Carini M, Romagnani S, Annunziato F. Frequency of regulatory T cells in peripheral blood and in tumour-infiltrating lymphocytes correlates with poor prognosis in renal cell carcinoma. BJU Int. 2010 Aug 24. doi: 10.1111/j.1464-410X.2010.09555.x.

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

46. Deschoolmeester V, Baay M, Van Marck E, Weyler J, Vermeulen P, Lardon F, Vermorken JB. Tumor infiltrating lymphocytes: an intriguing player in the survival of colorectal cancer patients. BMC Immunol. 2010 Apr 12;11:19.

47. Pölcher M, Braun M, Friedrichs N, Rudlowski C, Bercht E, Fimmers R, Sauerwald A, Keyver-Paik MD, Kübler K, Büttner R, Kuhn WC, Hernando JJ. Foxp3(+) cell infiltration and granzyme B(+)/Foxp3(+) cell ratio are associated with outcome in neoadjuvant chemotherapy-treated ovarian carcinoma. Cancer Immunol Immunother. 2010 Jun;59(6):909-19.

48. Suzuki H, Chikazawa N, Tasaka T, Wada J, Yamasaki A, Kitaura Y, Sozaki M, Tanaka M, Onishi H, Morisaki T, Katano M. Intratumoral CD8(+) T/FOXP3 (+) cell ratio is a predictive marker for survival in patients with colorectal cancer. Cancer Immunol Immunother. 2010 May;59(5):653-61.

49. Chew V, Tow C, Teo M, Wong HL, Chan J, Gehring A, Loh M, Bolze A, Quek R, Lee VK, Lee KH, Abastado JP, Toh HC, Nardin A. Inflammatory tumour microenvironmentis associated with superior survival in hepatocellular carcinoma patients. JHepatol. 2010 Mar;52(3):370-9.

50. Kloor M. Lymphocyte infiltration and prognosis in colorectal cancer. Lancet Oncol. 2009 Sep;10(9):840-1.

51. Oble DA, Loewe R, Yu P, Mihm MC Jr. Focus on TILs: prognostic significance of tumor infiltrating lymphocytes in human melanoma. Cancer Immun. 2009 Apr 2;9:3.

52. Uppaluri R, Dunn GP, Lewis JS Jr. Focus on TILs: prognostic significance of tumor infiltrating lymphocytes in head and neck cancers. Cancer Immun. 2008 Dec 4;8:16.

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

54. Leffers N, Gooden MJ, de Jong RA, Hoogeboom BN, ten Hoor KA, Hollema H, Boezen HM, van der Zee AG, Daemen T, Nijman HW. Prognostic significance of tumor-infiltrating T-lymphocytes in primary and metastatic lesions of advanced stage ovarian cancer. Cancer Immunol Immunother. 2009 Mar;58(3):449-59.

55. Al-Shibli KI, Donnem T, Al-Saad S, Persson M, Bremnes RM, Busund LT. Prognostic effect of epithelial and stromal lymphocyte infiltration in non-small cell lung cancer. Clin Cancer Res. 2008 Aug 15;14(16):5220-7.

56. Galon J, Costes A, Sanchez-Cabo F, Kirilovsky A, Mlecnik, B, Lagorce-Pages C, Toslini M, Camus M, Berger A, Wind P, Zinzindohoue F, Bruneval P, Cugnenc P,

Trajanoski Z, Fridman W, and Pages F. Type, density, and location if immune cells within human colorectal tumors predicts clinical outcome. Science. 2006 313:1960-64.

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

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

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

60. Okazaki T, Maeda A, Nishimura H, Kurosaki T, Honjo T. PD-1 immunoreceptor inhibits B cell receptor-mediated signaling by recruiting src homology 2-domain-containing tyrosine phosphatase 2 to phosphotyrosine. Proc Natl Acad Sci USA 2001;98:13866-71.

61. Zhang X, Schwartz JC, Guo X, Bhatia S, Cao E, Lorenz M, et al. Structural and functional analysis of the costimulatory receptor programmed death-1. Immunity 2004;20:337-47

62. Chemnitz JM, Parry RV, Nichols KE, June CH, Riley JL. SHP-1 and SHP-2 associate with immunoreceptor tyrosine-based switch motif of programmed death 1 upon primary human T cell stimulation, but only receptor ligation prevents T cell activation. J Immunol 2004;173:945-54.

63. Sheppard KA, Fitz LJ, Lee JM, Benander C, George JA, Wooters J et al. PD-1 inhibits T-cell receptor induced phosphorylation of the ZAP70/CD3zeta signalosome and downstream signaling to PKCtheta. FEBS Lett 2004;574:37-41.

64. Riley JL. PD-1 signaling in primary T cells. Immunol Rev 2009;229:114-25.

65. Parry RV, Chemnitz JM, Frauwirth KA, Lanfranco AR, Braunstein I, Kobayashi SV, et al. CTLA-4 and PD-1 receptors inhibit T-cell activation by distinct mechanisms. Mol Cell Biol 2005;25:9543-53

66. Agata Y, Kawasaki A, Nishimura H, Ishida Y, Tsubata T, Yagita H, et al. Expression of the PD-1 antigen on the surface of stimulated mouse T and B lymphocytes. Int Immunol 1996;8(5):765-72.

67. Vibhakar R, Juan G, Traganos F, Darzynkiewicz Z, Finger LR. Activation induced expression of human programmed death-1 gene in T-lymphocytes. Exp Cell Res 1997;232:25-8.

Product: MK-3475 1
Protocol/Amendment No.: 001-01

SUMMARY OF CHANGES

PRIMARY REASON FOR THIS AMENDMENT:

The primary reason for this amendment is changes resulting from discussions with the Food and Drug Administration (FDA) following review of the MK-3475 Investigational New Drug (IND) application and protocol. The main changes are:

- Addition of Grade 5 (death) to the list.
- Specification of Febrile Neutropenia and Grade 3 and 4 criteria.
- Revised thrombocytopenia criteria.
- Discontinuation of any patient who experiences a DLT in Cycle 1.
- Extended testing for MK-3475 antibodies and MK-3475 pharmacokinetics (PK) after study discontinuation (described under Other Changes Included in the Amendment).

Section 2.4.2 Definition of Dose Limiting Toxicities:

Old Language:

4. Neutropenia that is:
   - Grade 3 or 4 (i.e., ANC <1000 per mm^3) and associated with fever (oral temperature ≥39ºC) requiring antibiotic therapy.
   - Grade 4 which lasts >7 days or leads to use of therapeutic G-CSF
5. Grade 4 thrombocytopenia (i.e., platelets <25,000 per mm^3) or Grade 3 thrombocytopenia (i.e., platelets <50,000 per mm^3) with bleeding.

If a patient experiences a DLT in Cycle 1, the patient will be discontinued from study therapy unless the Investigator considers it in the best interest of the patient to continue on study (e.g., in case of tumor regression, symptomatic disease improvement, and/or if the type of DLT is viewed as preventable in subsequent cycles, e.g., by premedication). Such cases will require approval by the SPONSOR prior to continuation on study therapy.

New Language:

4. *Febrile* neutropenia *Grade 3 or Grade 4*:

- Grade 3 is defined as ANC <1000/mm^3 *with a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of ≥38 degrees C (100.4 degrees F) for more than one hour*
- Grade 4 is defined as ANC <1000/mm^3 *with a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of ≥38 degrees C (100.4 degrees F) for more than one hour, with life-threatening consequences and urgent intervention indicated.*

5. Thrombocytopenia <25,000/mm^3 *if associated with*:

   - *A bleeding event which does not result in hemodynamic instability but requires an elective platelet transfusion, or*
   - *A life-threatening bleeding event which results in urgent intervention and admission to an Intensive Care Unit.*

6. Grade 5 toxicity (i.e., death).

If a patient experiences a DLT in Cycle 1, *study therapy will be discontinued*.

OTHER CHANGES INCLUDED IN THE AMENDMENT:

Typographical errors and inconsistencies were corrected throughout the document. These changes are not listed here.

Additional changes to the protocol include the following:

Section 1.7 Study Flow Chart

Addition of Follow-up Visit column, including appropriate notation for pharmacokinetic, anti-MK-3475 antibodies and tumor imaging collections.

Relabeling of End of Study Visit to Safety Follow-up Visit and updated throughout the Study Flow Chart and protocol. Locations of text that was changed to reflect the new visit label is not listed here.

Removal of 12-lead electrocardiogram (ECG) on Day 15, Cycle 1.

Addition of lymphocyte subtyping (FACS) testing to the Safety Follow-up Visit.

Addition of immunoglobulin testing to the Safety Follow-up Visit.

Addition of footnote 25 and 26.

Correct "Auto MK-3475 Antibodies" to "Anti MK-3475 Antibodies".

Old Language:

Footnote 2: End of Study visit should be conducted approximately 4 weeks after the last dose of study therapy or before the initiation of a new treatment, whichever comes first. Patients who are discontinued from the study due to an unacceptable drug-related adverse event will be followed until the resolution of the AE to Grade 0-1 or stabilization or until beginning of a new therapy for their cancer, whichever occurs first. In patients who discontinue before 24 months of study therapy and have no documented disease progression, every effort should be made to follow the patient (1) for approximately 6 months without disease progression, (2) until start of a new anti-cancer treatment, (3) until documented disease progression, or (4) until death, whichever occurs first.

Footnote 7: Electrocardiogram (ECG) should be performed pre and post infusion on Day 1 of each cycle. The ECG post infusion should be performed within +5 minutes following the completion of infusion.

Footnote 9: See Appendix 6.1 for list of laboratory tests. Routine laboratory tests (e.g., CBC with differential; comprehensive serum chemistry panel; PT/INR and aPTT; thyroid function tests such as T3, T4, TSH; immunoglobulins; urinalysis; urine and serum β-HCG; auto-antibodies such as described in footnote 17; tumor markers) will be performed by the local study site laboratory. Other laboratory tests will be performed by a central laboratory. Patient treatment and overall management decisions will be based on local laboratory data.

Footnote 10: PT/INR and aPTT should be collected at baseline and at the mandatory end of study visit after discontinuation of study therapy. Coagulation parameters should be determined throughout the study if clinically indicated.

Footnote 12: Limited to Part A of the study: Cycle 1: predose; Days 3, 8, 15, 22 and 29; Cycle 2 and subsequently every other cycle in the first 12 months on study at predose.

Footnote 13: T3, FT4, TSH; at every cycle.

Footnote 14: Collection for analysis of IgG and IgM at baseline, in Part A on day 29 of Cycle 1, at predose every other cycle in first 12 months, approximately every 2 months in second 12 months, and at end of study visit.

Footnote 15: In Part A of the study: Cycle 1: predose; Days 3, 8, 15, 22 and 29.

Footnote 16: Cycle 1: predose, 1 h +/- 30 minutes after end of infusion, and approximately 6 hours after start of infusion. Subsequently to be collected at predose approximately every month until 6 months of study therapy. Includes multi-analysis panels (MAPs): Cytokine MAPAv1.0 and MAPBv1.0, and OncologyMAPv1.0 from RulesBasedMedicine.

Footnote 17: Collected at predose of Cycle 1 and Cycle 2, and then of every other cycle following Cycle 2. Include antinuclear antibodies; anti-DNA antibodies; antithyroglobulin antibodies; antimicrosomal antibodies; and anticardiolipin antibodies. When a blood sample is positive for antinuclear antibodies (i.e., titer of ≥40), it will be tested for antibodies against extractable nuclear antigens.

Footnote 18: Collected at predose of Cycle 1 and Cycle 2, and then at predose of every other cycle. In patients who discontinue study therapy before 6 months, every effort should be made to analyze anti-MK-3475 antibodies approximately 6 months after the first dose.

Footnote 19: Collected at baseline and every month at predose until 6 months of study therapy.

Footnote 20: Refer to Details of Sampling for Pharmacokinetics and Pharmacodynamics flow chart for timing. Procedures for collection of samples are described in the procedures manual.

Footnote 21: Tumor markers (if appropriate) will be collected within 14 days prior to Cycle 1/Day 1, and while on study approximately every 2 months in the first 12 months and approximately every 3 months in the 2nd year.

New Language:

Footnote 2: *The mandatory Safety Follow-Up* Visit should be conducted approximately 4 weeks after the last dose of study therapy or before the initiation of a new treatment, whichever comes first. Patients who are discontinued from the study due to an unacceptable drug-related adverse event will be followed until the resolution of the AE to Grade 0-1 or stabilization or until beginning of a new therapy for their cancer, whichever occurs first.

Footnote 7: Electrocardiogram (12-lead ECG) should be performed *at baseline, at the time of PK blood collection for PK (Cmax) within 30 minutes after the end of the first infusion of MK-3475, after infusion of MK-3475 in every other cycle (within 30 minutes after the end of infusion), and at the mandatory Safety Follow-up Visit.*

Footnote 9: See Appendix 6.1 for list of laboratory tests. Routine laboratory tests (e.g., CBC with differential; comprehensive serum chemistry panel; PT/INR and aPTT; thyroid function tests such as T3, T4, TSH; immunoglobulins; urinalysis; urine and serum β-HCG; tumor markers *where appropriate and feasible*) will be performed by the local study site laboratory *or their contract laboratory*. Other laboratory tests will be performed by a central laboratory. Patient treatment and overall management decisions will be based on local laboratory data.

Footnote 10: PT/INR and aPTT should be collected at baseline and at the mandatory *Safety Follow-up Visit* after discontinuation of study therapy. Coagulation parameters should be determined throughout the study when clinically indicated. *PT/INR and aPTT will be analyzed by the local study site laboratory.*

Footnote 12: Limited to Part A of the study: Cycle 1: predose; Days 3, 8, 15, 22 and 29; Cycle 2 and subsequently every other cycle in the first 12 months on study at predose; at the mandatory *Safety Follow-up Visit*. *FACS analysis of lymphocyte subpopulations will be performed in a central laboratory.*

Footnote 13: T3, FT4, TSH; at every cycle, *and at the mandatory Safety Follow-up Visit. Analysis of T3, FT4 and TSH will be performed by a central laboratory.*

Footnote 14: Analysis of IgG and IgM at baseline, in Part A on day 29 of Cycle 1, at predose every other cycle in first 12 months, approximately every 2 months in second 12 months, and at *Safety Follow-up Visit*. *Analysis will be performed by the local study site laboratory*.

Footnote 15: In Part A of the study: Cycle 1: predose; Days 3, 8, 15, 22 and 29. *The analysis will be performed by a central laboratory.*

Footnote 16: Cycle 1: predose, 1 h +/- 30 minutes after end of infusion, and approximately 6 hours after start of infusion. Subsequently to be collected at predose approximately every month until 6 months of study therapy. Includes multi-analysis panels (MAPs) *such as* Cytokine MAPAv1.0 and MAPBv1.0, and OncologyMAPv1.0 from RulesBasedMedicine. *Analysis of cytokines/chemokines will be performed by a central laboratory.*

Footnote 17: Collected at predose of Cycle 1 and Cycle 2, and then of every other cycle following Cycle 2. Include antinuclear antibodies; anti-DNA antibodies; antithyroglobulin antibodies; antimicrosomal antibodies; and anticardiolipin antibodies. When a blood sample is positive for antinuclear antibodies (i.e., titer of ≥40), it will be tested for antibodies against extractable nuclear antigens. *Analysis will be performed by a central laboratory.*

Footnote 18: Blood for anti-MK-3475 antibodies should be collected within 24 hours before start of infusion in Cycle 1 and Cycle 2 and then in every other subsequent cycle, and at the mandatory *Safety Follow-up Visit. Every effort should be made to collect additional blood samples for anti-MK-3475 antibodies approximately every 2 months after the Safety Follow-up Visit for up to 6 months from the last dose of MK-3475 or until start of a new anti-cancer therapy, whichever occurs first. Analysis will be performed by a central laboratory.*

Footnote 19: Collected at baseline and every month at predose until 6 months of study therapy. *Analysis will be performed by a central laboratory.*

Footnote 20: For timing refer to the following chart on Details of Sampling for Pharmacokinetics and Pharmacodynamics flow chart for timing. Procedures for collection of samples are described in the procedures manual.

Footnote 21: Standard tumor markers (as appropriate for a given tumor type) will be collected within 14 days prior to Cycle 1/Day 1, and while on study approximately every 2 months in the first 12 months and approximately every 3 months in the 2nd year. *Analysis will be performed by the local study site laboratory where feasible. If not feasible, tests will be performed by a central laboratory.*

Footnote 25: *In patients in Part A, every effort should be made to collect blood samples for PK for up to 6 months after the last dose as per the guidelines in the "Details of Sampling for Pharmacokinetics and Pharmacodynamics" flow chart. In patients in Part A and Part B, every effort should be made to collect blood samples for anti-MK-3475 antibodies for up to 6 months as per the guidelines in footnote 18. In patients in Part A and Part B who discontinue study therapy early without documented disease progression, every effort should be made to continue monitoring their disease status by radiologic imaging following the guidelines described in footnote 22; the monitoring of disease status should continue (1) until 2 years from start of study treatment, (2) for approximately 6 months without disease progression, (3) until start of a new anti-cancer treatment, (4) until documented disease progression, (5) until death, or, whichever occurs first.*

Footnote 26: *Procedures listed on Day 1 are for patients in both Part A and B (unless otherwise noted). Procedures listed from Day 2 through Day 29 of the 28 Day Cycle 1 are only for patients in Part A. Cycle 1 for patients in Part B is 14 days.*

Section 1.7 Details of Sampling for Pharmacokinetics and Pharmacodynamics

Time points for post-dose corrected to "End infusion to +30 min" for Cycle 1 and Cycle 2 and Additional Cycles.

Addition of Follow-up Visit column, including appropriate notation for pharmacokinetic collections.

Old Language:

General footnote:

- Actual drug dosing and PK/PD sampling times have to be documented by the sites and will be captured in the database.

Footnote 2: Immediately at end of MK-3475 infusion. Allowable window is +5 minutes. Sample collection must be from opposite arm to that used for study drug infusion. If drug was administered via a central venous catheter, sample collection for PK should be from a different site.

New Language:

General footnote:

- Actual *times of* drug dosing and PK/PD sampling have to be documented by the sites and will be captured in the database.
- *PK and PD analyses will be performed by a central laboratory*.

Footnote 2: Sample collection must be from opposite arm to that used for study drug infusion. If drug was administered via a central venous catheter, sample collection for PK should be from a different site.

Footnote 8: *In patients in Part A, every effort should be made to collect additional PK samples every 4-8 weeks after the Safety Follow-up Visit for up to 6 months from the last dose of MK-3475 or until start of a new anti-cancer therapy, whichever occurs first.*

Section 2.3 Patient Exclusion Criteria

Old Language:

Female patients enrolled in the study, who are not free from menses for >2 years, post hysterectomy / oophorectomy, or surgically sterilized, must be willing to use 2 adequate barrier methods of contraception to prevent pregnancy or to abstain from heterosexual activity throughout the study, starting with Visit 1 through 30 days after the last dose of study therapy. Approved contraceptive methods include for example; intra uterine device, diaphragm with spermicide, cervical cap with spermicide, male condoms, or

female condom with spermicide. Spermicides alone are not an acceptable method of contraception.

New Language:

Female patients enrolled in the study, who are not free from menses for >2 years, post hysterectomy / oophorectomy, or surgically sterilized, must be willing to use *either* 2 adequate barrier methods *or a barrier method plus a hormonal method of* contraception to prevent pregnancy or to abstain from heterosexual activity throughout the study, starting with Visit 1 through 30 days after the last dose of study therapy. Approved contraceptive methods include for example; intra uterine device, diaphragm with spermicide, cervical cap with spermicide, male condoms, or female condom with spermicide. Spermicides alone are not an acceptable method of contraception.

Section 2.4 Summary of Study Design

Addition of last paragraph.

New Language:

In patients who discontinue study therapy early without documented disease progression, every effort should be made to continue monitoring their disease status by radiologic imaging following the guidelines described in the Study Flow Chart (Section 1.7) and Section 3.2.5.4.13 (Duration of Follow-up).

Section 3.2.5.3 Registration/Enrollment

Clarification of registration added.

New Language:

Treatment will begin within 7 days from the date of registration *(i.e., approval of patient enrollment by SPONSOR and subsequent assignment of an allocation number).*

Section 3.2.5.4.12 Safety Follow-up Visit

Old Language:

At the time the patient is discontinued from treatment, the End of Study Visit procedures and assessment should be performed as listed in the Study Flow Chart (Section 1.7). The patient will be monitored for adverse events up to 30 days after discontinuation from the study or resolution of toxicity to Grade 0-1, whichever occurs later. Patients who start another cancer therapy before the planned End of Study Visit at approximately 30 days after last administration of study drug will be no longer monitored for adverse events in

this study. The discontinuation visit should occur prior to the patient receiving any non-study cancer therapy.

New Language:

After the patient is discontinued from *study therapy, a mandatory Safety Follow-Up* Visit *should be performed approximately 30 days after the last infusion of study medication.* Procedures and assessments *performed at the Safety Follow-Up* Visit should *follow the guidelines described* in the Study Flow Chart (Section 1.7). The patient will be monitored for adverse events up to *the mandatory Safety Follow-Up Visit* or *to* resolution of toxicity to Grade 0-1, whichever occurs later. *In* patients who start another cancer therapy before 30 days after discontinuation of study therapy, the *Safety Follow-Up Visit should occur prior to the patient receiving another cancer therapy. Once a patient starts another cancer therapy, monitoring for adverse events in the present study will discontinue.*

Section 3.2.5.4.13 Duration of Follow-up

Old Language:

In patients who discontinue before 24 months of study therapy and have no documented disease progression, every effort should be made to follow the patient (1) for approximately 6 months without disease progression, (2) until start of a new anti-cancer treatment, (3) until documented disease progression, or (4) until death, whichever occurs first. The interval of imaging studies should follow the guidelines as the Study Flow Chart (Section 1.7; footnote 22).

New Language:

In patients who discontinue *study therapy early without documented disease progression, every effort should be made to continue monitoring their disease status by radiologic imaging following the guidelines described in the Study Flow Chart (Section 1.7; footnote 22); the monitoring of disease status should continue (1) until 2 years from start of study treatment, (2) for approximately 6 months without disease progression, (3) until start of a new anti-cancer treatment, (4) until documented disease progression, (5) until death, or, whichever occurs first.*

In patients in Part A, every effort should be made to collect blood samples for PK for up to 6 months after the last dose as per the guidelines in Section 1.7 (flow chart on "Details of Sampling for Pharmacokinetics and Pharmacodynamics".

In patients in Part A and Part B, every effort should be made to collect blood samples for anti-MK-3475 antibodies for up to 6 months as per the guidelines described in the Study Flow Chart (Section 1.7, footnote 18).

Section 3.3.1.1 Radiographic Assessment

Old Language:

The baseline tumor imaging (CT or MRI, with a preference for CT) examinations must be performed within 30 days before enrollment. Patients continuing on study will have follow-up imaging performed approximately every 2 months in the first 12 months and approximately every 3 months in the second year. The same imaging technique should be used in a patient throughout the study. After first documentation of response (complete response or partial response), imaging performed at the next regularly scheduled time point (e.g., 2 months later in the first 12 months of study therapy) will be used for response confirmation.

New Language:

The baseline tumor imaging (CT or MRI, with a preference for CT; *or lung x-ray*) examinations must be performed within 30 days before enrollment. Patients continuing on study will have follow-up imaging performed approximately every 2 months in the first 12 months and approximately every 3 months in the second year. *The same guidelines apply to patients who discontinue study therapy early with no documented disease progression, following the specific instructions described in the Study Flow Chart (Section 1.7) and in Section 3.2.5.4.13.*

The same imaging technique should be used in a patient throughout the study. After first documentation of response (complete response or partial response), imaging performed at the next regularly scheduled time point (e.g., 2 months later in the first 12 months of study therapy) will be used for response confirmation.

Section 3.4.5 Immediate Reporting of Adverse Experiences to the SPONSOR

Old Language:

Any serious adverse experience should be recorded and reported within 24 hours or, at least, on the following working day to Global Pharmacovigilance via facsimile (found in the administrative binder) using the following fax number:

Fax: 908-740-2169

New Language:

Any serious adverse experience should be recorded and reported within 24 hours or, at least, on the following working day to *the SPONSOR* via facsimile (found in the administrative binder).

Section 3.5.5.2 Pharmacokinetic Analysis

Old Language:

MK-3475 pharmacokinetic variables (e.g., C_{max}, T_{max}, C_{trough} and AUC) will be calculated as appropriate and summary statistics will be provided. Graphical, non-compartmental and potentially exploratory compartmental analyses will be used for the analysis of the pharmacokinetic data.

New Language:

MK-3475 pharmacokinetic variables (e.g., C_{max}, T_{max}, C_{trough} and AUC) will be calculated as appropriate and summary statistics will be provided. Graphical, non-compartmental and potentially exploratory compartmental analyses will be used for the analysis of the pharmacokinetic data. *An exploratory analysis of a potential relationship between dose level, pharmacokinetic variables and clinical safety and anti-tumor activity will be performed as appropriate*.

Section 3.5.5.3 Pharmacodynamic Analysis

Old Language:

PD-1 receptor occupancy and PD-1 target modulation will be analyzed as appropriate and summary statistics will be provided.

New Language:

PD-1 receptor occupancy and PD-1 target modulation will be analyzed as appropriate and summary statistics will be provided. *An exploratory analysis of a potential pharmacokinetic-pharmacodynamic relationship will be performed as appropriate.*

Appendix 6.1 Laboratory Safety Tests/Screening/Baseline Labs

Clarification added regarding location of laboratory analysis.

Product: MK-3475 1
Protocol/Amendment No.: 001-02

SUMMARY OF CHANGES

PRIMARY REASON FOR THIS AMENDMENT:

The primary objective for this amendment is the revision of Part B to:

1) Characterize the safety profile of MK-3475 at the recommended phase 2 dose (RP2D) determined in Part A.

2) Evaluate the anti-cancer activity of MK-3475 in patients with advanced melanoma (MEL).

3) Investigate the correlation of biomarkers such as PD-L1 and anti-tumor activity of MK-3475.

Implementation of these objectives necessitates the following changes to the protocol:

- Increase in Part B sample size from 14 to 66 patients.
- Limit Part B enrollment to only those patients with unresectable MEL.
- Mandate on pre-treatment fresh tumor biopsies as a study entry criterion.
- A complete revision of Part B procedures, resulting in changes to all sections throughout the protocol Core and Details sections that reference Part B. These changes include alterations to study endpoints, procedures and analysis for Part B.

Because of the extensive changes made to execute the above objectives, a complete review is warranted of all aspects of Part B. Consequently, specific changes for Part B are not listed in the Summary of Changes.

OTHER CHANGES INCLUDED IN THE AMENDMENT:

Throughout the protocol, procedures have been separately listed for Part A and Part B. Changes specific to the conduct of Part A are listed here. Part B text should be reviewed in their entirety throughout the protocol.

In addition, typographical errors and inconsistencies were corrected throughout the document and are not listed here. Protocol sections that include changes relevant to both Part A and B, but do not impact study conduct for Part A are not listed here (e.g., 3.1.2 Rationale for This Study, 3.1.3 Rationale for Dose, etc) and should be reviewed in their entirety.

Throughout the protocol, the maximum tolerated dose is no longer referred to as "preliminary".

Section 1.1 Title

Phase I Study of Single Agent MK-3475 in Patients with *Progressive Locally Advanced or Metastatic Carcinomas and Melanoma.*

Section 1.2 Indication

*For Part A, p*atients with a histologically or cytologically confirmed diagnosis of any type of carcinoma *or of melanoma (MEL)* who have progressive locally advanced or metastatic disease.

For Part B, patients with a histologically confirmed diagnosis of MEL with progressive locally advanced or metastatic disease that is not amenable to definitive local therapy with curative intent.

- *Note: A diagnosis of MEL which is only based on cytology (e.g., from a fine needle biopsy or a malignant effusion) is not sufficient for eligibility in Part B.*

Section 1.4 Summary of Study Design

This is a*n* open-label, non-randomized *Phase I* study of intravenous (IV) MK-3475 in patients with locally advanced or metastatic carcinomas or MEL. *Part A of* the study will use a *traditional* 3+3 design *for dose escalation.* Cohorts of 3-6 patients will be enrolled sequentially at escalating doses of 1.0, 3.0 and 10 mg/kg. Dose escalation will continue until identification of *MTD,* up to *a maximum* dose of 10 mg/kg. In Part B, patients with MEL will be enrolled *at the preliminary RP2D to more fully characterize* the tolerability *and safety profile* of the dose and for preliminary evaluation of anti-tumor activity in MEL.

Section 1.5 Sample

A *total* of approximately *84* eligible patients will be enrolled in this study, with *9 to* 18 patients in Part A and approximately *66* patients in Part B.

Section 1.7 Flow Chart

The study flow chart has been split into flow charts specific for Part A and Part B. The following changes were applied to the Study Flow Chart specific for Part A:

- Removal of comprehensive serum chemistry panels and CBC with differential testing from Cycle 1/Day 1.
- Clarification of "Urine or Serum β-HCG" to be pregnancy testing.
- Deleted Footnote 26.

- References to Part B of the study were removed from footnotes and table.
- Footnote 18: Collection of anti-MK-3475 antibodies may now be collected up to 24 hours before the start of infusion.
- Testing for HIV, Hepatitis B and C will now be tested at Screening (addition of footnote 21).
- Footnotes 21 and up have been renumbered, each increasing by an increment of 1.
- Clarification of the term "baseline" in footnotes 7, 10, 14, and 19 to ensure consistency within the flow chart.
- Adverse experiences will be collected during the follow-up.

Section 2.1.1 Primary Objectives

1) To evaluate *and characterize* the tolerability *and safety profile* of *single agent* MK-3475 *in* adult patients with *unresectable advanced carcinoma* or MEL, *and to determine a RP2D for subsequent testing.*

   Hypothesis: Intravenous administration of single agent MK-3475 will have acceptable safety and tolerability. ~~and the overall data on dose limiting toxicity (DLT), MTD, safety profile, PK and PD will identify a dose of MK-3575 which is considered safe for evaluation in subsequent efficacy studies.~~

2) To evaluate anti-tumor activity of MK-3475 in MEL.

   Hypothesis: Single agent MK-3475 will show a response rate (RR) and/or disease control rate (DCR) in MEL that merits further investigation (for details, see Section 3.5, Statistical Analysis Plan).

Section 2.1.2 Secondary Objectives

2) To evaluate target engagement and modulation in peripheral blood (PD-1 receptor occupancy and modulation of receptor activity).

3) To investigate the relationship between candidate efficacy biomarkers and anti-tumor activity of MK-3475:

- *To evaluate the correlation between PD-L1 expression levels and anti-tumor activity of MK-3475.*
- *To investigate other biomarkers (e.g., tumor infiltrating lymphocytes, PD-L2, PD-1; ribonucleic acid (RNA) signature profiles) that may correlate with tumor responses.*

- *To evaluate differences in tumor tissue characteristics in biopsies taken during or post-treatment with MK-3475 versus baseline.*

4) To evaluate response duration, progression-free-survival and overall survival of patients who are treated with MK-3475.

Section 2.1.3 Tertiary Objectives

1) To examine concordance between archival tumor tissues, formalin-fixed, paraffin-embedded tissue (FFPET) and fresh frozen tumor tissue with respect to PD-L1 expression and other candidate efficacy biomarkers.

The second and third tertiary objectives were removed.

Section 2.2 Patient Inclusion Criteria

1) *In Part A of the study*, patients must have a histological or cytological diagnosis of MEL or any type of carcinoma, progressive metastatic disease, or progressive locally advanced disease not amenable to local therapy:

- Please note: *T*umor types of primary interest in *Part A include but are not limited to* malignant MEL, RCC, hepatocellular carcinoma, non-small cell lung cancer, gastric carcinoma, ovarian carcinoma and colorectal carcinoma.

- *P*atients must have failed established standard medical anti-cancer therapies for a given tumor type or have been intolerant to such therapy, or in the opinion of the Investigator have been considered ineligible for a particular form of standard therapy on medical grounds.

5) Patient must have a performance status *of 0 or 1* on the *Eastern Cooperative Oncology Group* (ECOG) Performance Scale (Appendix 6.2).

9) Female patients enrolled in the study, who are not free from menses for >2 years, post hysterectomy / oophorectomy, or surgically sterilized, must be willing to use either 2 adequate barrier methods *or* a barrier method plus a hormonal method of contraception to prevent pregnancy or to abstain from heterosexual activity throughout the study, starting with Visit 1 through *90* days after the last dose of study therapy. Approved contraceptive methods include for example; intra uterine device, diaphragm with spermicide, cervical cap with spermicide, male condoms, or female condom with spermicide. Spermicides alone are not an acceptable method of contraception.

Section 2.3 Patient Exclusion Criteria

3) Patient is expected to require any other form of antineoplastic therapy while on study. ~~Exempted are patients with prostate cancer who are on luteinizing hormone-releasing~~

~~hormone (LHRH) agonists and continue on the same dose and type of LHRH agonists.~~

4) Patient is on chronic systemic steroid therapy ~~at doses >10 mg/day,~~ or on any other form of immunosuppressive medication.

6) Patient has a known history of a hematologic malignancy, primary brain tumor or sarcoma, *or of another primary solid tumor*, unless the patient has undergone potentially curative therapy with no evidence of that disease for 5 years.

    - *Note: The time requirement for no evidence of disease for 5 years does not apply to the tumor for which a patient is enrolled in the study. The time requirement does also not apply to patients who underwent successful definitive resection of basal cell carcinoma of the skin, superficial bladder cancer or in situ cervical cancer.*

7) Patient has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Patients with previously treated brain metastases may participate provided they are clinically stable for at least *8 weeks* ~~1 month~~ prior to study entry, ~~defined as: (1)~~ *have* no evidence of new or enlarging brain metastases and *are* ~~(2)~~ off steroids~~, or on a stable dose of steroids for at least 1 month.~~

10) Patient had prior therapy with an anti-PD-1 *antibody* ~~or anti-CTLA-4 antibody (T Cell co-stimulatory pathways)~~ or ~~any other~~ *an* antibody targeting *other immuno-regulatory receptors or mechanisms (with exception of ipilimumab in study Part B).*

    - *Examples of such antibodies include (but are not limited to) antibodies against IDO, PD-L1, IL-2R, GITR.*

12) Patient is ~~known to be~~ positive for Human Immunodeficiency Virus (HIV) *(HIV 1/2 antibodies)*, Hepatitis B *(HBsAg reactive)* or Hepatitis C ~~virus~~ *(HCV RNA (qualitative) is detected).*

Section 2.4.1 Summary of Study Design

Part A

Part A will use a 3+3 design and will enroll cohorts of 3-6 patients with MEL or any type of carcinoma sequentially at escalating doses of 1.0, 3.0 and 10 mg/kg. Dose escalation will continue until identification of a MTD, up to *a maximum* dose of 10 mg/kg.

Radiological assessment of tumor response status should be performed approximately every 2 months for the first 12 months of treatment and approximately every 3 months thereafter. (If considered more appropriate by the investigator, disease monitoring by radiological imaging can continue at 2-month intervals beyond the first 12 months.)

Patients will be monitored for safety, anti-MK-3475 antibodies and efficacy throughout the study. If available and consented by participating patients, archived tumor tissue will be collected. In Part A, fresh tumor biopsies may be performed for biomarker analysis in select patients with readily accessible tumor lesions and who consent to the biopsies. Ideally, follow-up biopsy should be taken from the same tumor lesion as the baseline biopsy.

In patients who discontinue study therapy early without documented disease progression, every effort should be made to continue monitoring their disease status by radiologic imaging following the guidelines described in Section 3.2.5.4.14 (Duration of Follow-up).

The primary data used for dose escalation and confirmation will be dose limiting toxicity (DLT) in Cycle 1 (see Section 3.2.5.4.7 for details).

Section 2.4.3 Treatment Plan

In patients *(Part A or Part B)* who *have* an AE *as* described in Section *3.2.5.4.9*, study therapy will be *withheld* until resolution of toxicity to Grade 0-1. In the event of insufficient resolution of toxicity 4 weeks after administration of study drug, study therapy will be discontinued. In patients who continue on study therapy after experiencing *such a treatment interruption*, the dosing interval in subsequent cycles will be increased *by 1* week *(e.g., to 3 weeks in patients who were on an every 2 week schedule). Two* dosing delays due to toxicity will be permitted. In the event of a *third* occurrence of a toxicity which would require dosing delay, study therapy will be discontinued *permanently*. (See Section *3.2.5.4.9* for detailed guidelines for dose modifications.)

Dose escalation in individual patients will not be permitted *in this study*.

Patients may continue on study therapy until disease progression, unacceptable toxicity, the withdrawal of consent, they require another form of cancer therapy as determined by the Investigator, *or* they require *>2* dosing *delays* of MK-3475 due to toxicity. *Continuation of study therapy beyond 2 years will be contingent on the continued availability of MK-3475 drug product.*

Section 3.2.2 Prohibited Medications

Patients may receive other medications that the Investigator deems to be medically necessary, with the specific exception of non-protocol specified chemotherapy, radiotherapy, immunotherapy, anti-neoplastic biological therapy or investigational agents other than MK-3475. Patients who *in the assessment by the investigator* require the use of any of the aforementioned treatments for clinical management should be removed from the study.

Patients are prohibited from receiving live vaccines within 30 days prior to the first dose of study therapy and while participating in study. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, seasonal flu, H1N1 flu, rabies, BCG, and typhoid vaccine.

Section 2.3 of the protocol (Exclusion Criteria) describes other medications which are prohibited in this study.

Section 3.2.4.2 Contraception

MK-3475 may have adverse effects on a fetus *in utero*. Furthermore, it is not known if MK-3475 has transient adverse effects on the composition of sperm. Non-pregnant, non-breast-feeding women may be enrolled if they are considered highly unlikely to conceive. Highly unlikely to conceive is defined as 1) surgically sterilized, or 2) postmenopausal (a woman who is ≥45 years of age and has not had menses for greater than 2 years will be considered postmenopausal), or *3) amenorrheaic for <2 years without a hysterectomy and oophorectomy and with a documented FSH value in the postmenopausal range, or 4*) not heterosexually active for the duration of the study, or *5*) heterosexually active and willing to use 2 methods of birth control (*which is also* recommended for the female partners of male patients). The 2 birth control methods can be 2 barrier methods or a barrier method plus a hormonal method to prevent pregnancy, used throughout the study starting with Visit 1 through *90* days after the last dose of study medication. Male patients enrolled in this study must also agree to use an adequate method of contraception starting with Visit 1 through 90 days after the last dose of study drug.

Section 3.2.5.4.7 Rules for Dose Escalation *in Part A*

DLTs observed in Cycle 1 will be used to determine escalation to the next dose level. The study is using a *traditional* 3+3 design *and the dose escalation rules are as follows*:

- An initial cohort of 3 patients is enrolled.
- If 0/3 patients develops a DLT, escalation to the next dose will occur.
- If 1/3 patients develops a DLT:
    - Another 3 patients will be enrolled at this dose level.
        - If 0 of the 3 new patients develops a DLT (for a total of 1/6 patients with a DLT at this dose level), escalation to the next dose level will occur.
        - If ≥1 of the 3 new patients develops a DLT (for a total of ≥2/6 patients with a DLT at this dose level), the dose escalation stage of the trial will be terminated, *and the dose directly below* the current dose will be considered the MTD.
- If ≥2/3 patients develop a DLT, the dose escalation stage of the trial will be terminated, *and* the dose directly below the current dose will be considered the MTD.

It is conceptually acceptable to de-escalate to an intermediate, not pre-defined and not previously-studied dose, if evaluation of toxicity at such a dose is desired. If this approach is taken, 3 new patients should be enrolled at the new intermediate dose, and the aforementioned rules should be used to determine further enrollment at this dose level.

The highest dose to be tested during dose escalation is 10 mg/kg. If 0/3 patients or ≤1/6 patients develop a DLT at that dose, then 10 mg/kg is considered the MTD.

Section 3.2.5.4.8 Preliminary RP2D for Use in Part B

Additional patients (up to 6) may be enrolled at preliminary RP2D in Part A if more robust PK characterization of MK-3475 is deemed warranted.

Section 3.2.5.4.9 Guidelines for Dose Modifications

Please review, the entire section is new text.

Section 3.2.5.4.10 Treatment Holidays

If considered in *a* patient's *best interest* by the Investigator, patients who have been on study therapy for *at least 24 weeks* may have *a* treatment holiday of up to *8* weeks in continuous duration in *every* 6-months period (i.e., 7-12 months; 13-18 months; 19-24 months, etc.). *Additional treatment holidays (in frequency and/or duration) require discussion with and approval by the sponsor on an individual basis. The same applies to patients who may develop disease progression while on a treatment holiday. If re-starting therapy with MK-3475 is considered in the best interest of such a patient by the investigator, this requires discussion with and approval by the sponsor.*

3.2.5.4.11 Supportive Care Guidelines

Please review Diarrhea and Infusion Reaction, each section is new text.

Neutropenia: Prophylactic use of colony-stimulating factors including Granulocyte Colony-Stimulating Factor (G-CSF), pegylated G-CSF or Granulocyte Macrophage Colony-Stimulating Factor GM-CSF is not allowed in this study. Therapeutic use of G-CSF is allowed in patients with Grade *3*-4 febrile neutropenia.

Thrombocytopenia: Transfusion of platelets may be used if clinically indicated. *ITP should be ruled out before initiation of platelet transfusion.*

3.2.5.4.12 Duration of Therapy

Treatment with MK-3475 may continue until one of the following events occurs:

- Documented disease progression

- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse experiences *(see Section 3.2.5.4.9)*
- Need for >2 dose delays due to toxicity as per the dose *modification* guidelines described in Section 3.2.5.4.9
- Patient withdraws consent
- If in the opinion of the Investigator, a change *or discontinuation* of therapy would be in the best interest of the patient
- Patient is lost to follow-up
- Pregnancy in patient

If a patient *discontinues* from the study, the procedures will be followed as described in Section *3.2.3.4.13 and 3.2.3.4.14.*

Continuation of study therapy beyond 2 years will be contingent on the continued availability of MK-3475 drug product.

Section 3.2.5.4.14 Duration of Follow-up

In all patients in Part A, every effort should be made to collect blood samples for PK every 4-8 weeks and antibodies to MK-3475 approximately every 2 months after last drug administration, for a total period of 24 weeks. In Part B, every effort should be made to collect blood samples for PK and antibodies to MK-3475 approximately every 12 weeks, for a total period of 24 weeks after last drug administration. The first collection of blood samples can be performed at the time of the mandatory Safety Follow-Up Visit.

For patients in Part A who *discontinued study therapy* without documented disease progression, every effort should be made to continue monitoring their disease status by radiologic imaging following the guidelines described in the Study Flow Chart (Section 1.7, *Part A). Disease monitoring* should continue *(1)* for approximately 6 months without disease progression, *(2)* until start of a new anti-cancer treatment, *(3)* until documented disease progression, or *(4)* until death, whichever occurs first.

Section 3.2.5.5 Interim Data Locks

Part A

An interim data clean and lock will occur when Part A patient accrual is complete and all patients have completed Cycle 1. The purpose of this interim lock is preliminary analysis of safety, PK and PD, and determination of MTD and preliminary RP2D.

At the time of interim locks in Part A and B, patients may continue study therapy as per protocol guidelines. Study procedures will continue to be followed as per protocol.

Section 3.3.1.2 Efficacy Endpoints

Part A

In Part A, overall response rate will be used to estimate anti-tumor activity. If applicable, response duration will be determined. Response duration will be measured from first documentation of response to first documentation of disease progression. No other efficacy endpoints will be analyzed in Part A.

Section 3.3.1.3 Radiographic Assessment

Part A

Part A patients who are on study therapy will have tumor imaging performed approximately every 2 months in the first 12 months and approximately every 3 months thereafter (see also Part A Study Flow Chart (Section 1.7), and Section 3.2.5.4.14.

After first documentation of CR or PR, imaging performed at the next regularly scheduled time point will be used for response confirmation.

Patients who discontinue study therapy without documented disease progression will have tumor imaging performed approximately every 3 months until (1) 6 months without disease progression, (2) start of a new anti-cancer treatment, (3) documented disease progression, or (4) death, whichever occurs first.

Section 3.4.1 Clinical and Laboratory Measurements in Safety

Vital signs, weight, physical examinations, ECOG performance status, ECGs and laboratory safety tests (e.g., PT/aPTT, urinalysis, CBC, serum chemistries, auto-antibodies, thyroid function, viral antigen reactions, cytokine / chemokine panels) will be obtained and assessed at designated intervals throughout the study (see Study Flow Chart, Section 1.7). *Special attention will be given to so-called immune-related adverse effects (e.g., gut, skin, liver, endocrine organs, others).*

Section 3.4.5.1 Serious Adverse Experiences

Any serious adverse experience, including death due to any cause, which occurs to any subject/patient entered into this study or within *180* days following cessation of treatment or within the established off therapy follow-up period for safety described in the protocol, whether or not related to the investigational product, must be reported within 24 hours to one of the individual(s) listed on the contact information page.

Appendix 6.1 Laboratory Safety Tests/Screening/Baseline Labs

Addition of absolute neutrophil count and absolute lymphocyte count to Hematology section.

Product: MK-3475 1
Protocol/Amendment No.: 001-03

SUMMARY OF CHANGES

PRIMARY REASON FOR THIS AMENDMENT:

The primary objectives of this amendment pertain to the revisions to Part A, Part B, and the addition of Part C. These changes are primarily encompassed by the following:

Part A: Additional characterization and assessment of pharmacokinetic (PK) and pharmacodynamic profiles via intra-patient dose escalation.

Part B: Evaluation of safety and anti-tumor activity in patients at 2 mg/kg and 10 mg/kg dosing every 3 weeks (Q3W).

Part C: Evaluation of safety and anti-tumor activity in patients with non-small cell lung cancer (NSCLC) at 10 mg/kg dosing every 3 weeks.

Implementation of these objectives necessitates the following changes to the protocol:

- Increase Part A sample size by 12 patients
- Increase Part B sample size from 66 patients to 116 patients by adding:
  - 15 additional ipilimumab naïve patients at 2 mg/kg, Q3W
  - 15 additional ipilimumab naive patients at 10 mg/kg, Q3W
  - 20 additional patients previously treated with ipilimumab at 10 mg/kg, Q3W
- Addition of a new cohort, Part C, sample size of 35 patients with NSCLC, including the addition of all Part C specific procedures.

OTHER CHANGES INCLUDED IN THE AMENDMENT:

Throughout the protocol, procedures have been separately listed for Part A, Part B and Part C. Changes specific to the conduct of Part A, B and C are listed here. Part C text should be reviewed in their entirety throughout the protocol.

In addition, typographical error and inconsistencies were corrected throughout the document and are not listed here. Protocol sections that include changes relevant to Part A, Part B and Part C, but do not impact study conduct of these Parts are not listed here (e.g., 1.3 Summary of Rationale, 3.1.2 Rationale for This Study, 3.1.3 Rationale for Dose) and should be reviewed in their entirety.

Product: MK-3475 2
Protocol/Amendment No.: 001-03

Section 1.1 Title

Phase I Study of Single Agent MK-3475 in Patients with Progressive Locally Advanced or Metastatic Carcinomas ~~and~~, Melanoma, *and Non-Small Cell Lung Carcinoma.*

Section 1.2 Indication

For Part B, patients with a histologically *or cytologically* confirmed diagnosis of MEL with progressive locally advanced or metastatic disease that is not amenable to definitive local therapy with curative intent.

For Part C, patients with a histologically or cytologically confirmed diagnosis of non-small cell lung cancer (NSCLC) with progressive locally advanced or metastatic disease after 2 prior systemic therapy regimens.

Section 1.3 Summary of Rationale

Redacted

1.4 Summary of Study Design

This is an open-label, non-randomized Phase I study of intravenous (IV) MK-3475 in patients with *progressive* locally advanced or metastatic carcinomas, *especially* MEL *or NSCLC*. Part A of the study will use a traditional 3+3 design for dose escalation. Cohorts of 3-6 patients will be enrolled sequentially at escalating doses of 1.0, 3.0 and 10 mg/kg. Dose escalation will continue until identification of MTD, up to a maximum dose of 10 mg/kg. *Once the dose escalation is completed, additional patients will be enrolled to more fully characterize the PK profile.* In Part B, patients with MEL will be enrolled at the preliminary RP2D*(s)* to characterize the tolerability and safety profile of the dose, and for preliminary evaluation of anti-tumor activity in MEL. *In Part C, patients with NSCLC will be enrolled at the preliminary RP2D(s) to characterize the tolerability and safety profile of the dose, and for preliminary evaluation of anti-tumor activity in NSCLC.*

1.5 Sample

A total of approximately *179* eligible patients will be enrolled in this study, with *approximately 28* patients in Part A, approximately *116* patients in Part B *and approximately 35 patients in Part C.*

In Part A, patients with any type of carcinoma may be enrolled, and patients may have non-measurable disease. *Patients in Part A will be distributed as follows:*

- *Dose escalation =10 patients*
- *Part A-1 (PK expansion at MTD) (up to 10 mg/kg Q2W): 6 patients*
- *Part A-2 (PK expansion, intra-patient dose escalation, Q3W): 12 patients.*

In Part B, only patients with MEL may be enrolled (metastatic MEL or patients with locally advanced disease and not candidates for surgical resection or a definitive local therapy), and patients must have measurable disease (see Section 2.2 and Appendix 6.5). *Part B will enroll approximately 116 patients distributed as described in Table 1-1:*

Table 1-1
Patient distribution in Part B

	10 mg/kg	2 mg/kg
Ipilimumab Naïve	61[1]	15[2]
Previously Ipilimumab Treated	40[1]	0
1 Includes patients with dosing schedules of Q2W and Q3W. 2 Dosing schedule is Q3W		

Enrollment of patients at 2 mg/kg in Part B will begin once all 10 mg/kg patients in Part B are enrolled. All patients enrolled after the approval of current amendment or approval of the administrative memo dated 06-Jan-2012, will be dosed Q3W.

Enrollment of the first 13 patients in Part B will be restricted to ipilimumab-naïve patients (which will serve as basis for the first interim analysis). *Upon approval of the current amendment*, the ipilimumab *treated* cohort is defined as patients who have progressive disease (PD) *within 6 months of the first dose of ipilimumab* (see eligibility criteria for details – Sections 2.2, 2.3). *Ipilimumab naïve patients are allowed up* to 2 prior systemic treatment regimens, one of which may have been prior treatment with a BRAF inhibitor. *Ipilimumab treated patients are allowed up to 3 prior systemic treatment regimens, one of which may have been prior treatment with a BRAF inhibitor.*

In Part C, 35 patients with NSCLC may be enrolled (progressive metastatic or locally advanced NSCLC after treatment with two prior systemic regimens), and patients must have measurable disease (see Section 2.2 and Appendix 6.5). All patients will be dosed Q3W.

Section 1.6 Dosage/Dosage Form, Route, and Dose Regimen

MK-3475 will be administered as a 30 minute IV infusion*, with a window of -5 and +10 minutes (except as indicated in Part A-2).*

Part A will consist of a dose escalation followed by additional analysis of PK and pharmacodynamic characteristics. Three dose levels of MK-3475 will be evaluated *in the dose escalation*: 1 mg/kg, 3 mg/kg and 10 mg/kg. To ascertain detailed PK analysis, the interval between the first and second dose in *the* Part A *dose escalation* will be 28 days. In subsequent cycles the dosing interval will be 14 days.

Additional patients will be enrolled in Part A to further explore PK characteristics. In Part A-1, six patients may be enrolled at the MTD up to 10 mg/kg, with a dosing interval every 2 weeks (Q2W). In Part A-2, 12 patients may be enrolled to further define PK characteristics with a dosing interval of every 3 weeks (Q3W) beginning with Cycle 2. In this cohort, lower doses (below 1 mg/kg) will be tested in order to explore relationship between PK and pharmacodynamics of MK-3475. PK and pharmacodynamic sample collection times for these 12 patients are presented in the table Details of Sampling for Pharmacokinetics and Pharmacodynamics for Part A-2 in Section 1.7. These patients will be enrolled following completion of enrollment in Part A-1. These patients will receive escalating doses in Cycle 1 as indicated in Table 1-2 and Table 1-3 below. Patients who do not complete Cycle 1 in Part A-2 may be replaced.

Table 1-2
Part A-2 Dose Titration

	N	***Day 1***	***Day 8***	***Day 22[1]***	***C2 and beyond[2]***
Cohort 1	*3*	*0.005 mg/kg[3]*	*0.3 mg/kg[3]*	*2.0 mg/kg*	*2.0 mg/kg*
Cohort 2	*3*	*0.02 mg/kg[3]*	*0.3 mg/kg[3]*	*2.0 mg/kg*	*2.0 mg/kg*
Cohort 3	*6*	*0.06 mg/kg[3]*	*1.0 mg/kg*	*10.0 mg/kg*	*10.0 mg/kg*

Patients will be randomly assigned to each cohort.
1 Day 22 sample = predose for Cycle 2/Day 1 for patients continuing in the study.
2 Dosing schedule C2 and beyond is Q3W.
3 Administered via IV push.

Table 1-3
Part A-2 Titration, Dose Matrix View

	Dose (mg/kg)						
Cohort	***0.005***	***0.02***	***0.06***	***0.3***	***1.0***	***2.0***	***10.0***
1 (n=3)	*x*			*x*		*x*	
2 (n=3)		*x*		*x*		*x*	
3 (n=6)			*x*		*x*		*x*
Total n[1]	*3*	*3*	*3*	*6*	*6*	*6*	*6*
Patients will be randomly assigned to each cohort. *1 Total is at a given dose across all cohorts and times.*							

In Part B MK-3475 will be administered at the preliminary RP2D*(s) as per Section 1.5. For patients who consent under protocol amendment 001-02, dosing will be repeated Q2W. For patients consented under protocol amendment 001-03, or following approval of the administrative memo dated 06-Jan-2012, dosing* in Part B *will be repeated Q3W*. Study therapy will continue until disease progression or unacceptable toxicity. *Patients who initiate therapy on the 2 week schedule will not switch to the 3 week schedule.*

In Part C, MK-3475 will be administered at preliminary RP2D, 10 mg/kg. Dosing in Part C will be repeated Q3W. Study therapy will continue until disease progression or unacceptable toxicity.

Dose escalation in individual patients will not be permitted in this study, *except where indicated in Part A-2.*

1.7 Study Flow Chart

Additional study flow charts have been placed into the protocol. Separate flow charts are provided for the following patient cohorts:

- Part A, Part A-1. This flow chart is now specific for patients in Part A and Part A-1. This flow chart is unchanged with the following exception:
  - Footnote 9: See Appendix 6.1 for list of laboratory tests. Routine laboratory tests (e.g., CBC with differential; comprehensive serum chemistry panel; urinalysis) will be performed by the local study site laboratory or their contract laboratory. *CBC, serum chemistry and urinalysis may be collected up to 48 hours prior to any Cycle "X", Day 1 dosing.*
- Part A-2. This flow chart is entirely new.

- Details of Sampling for Pharmacokinetics and Pharmacodynamics for Part A and Part A-1. This flow chart is now specific for patients in Part A and Part A-1. Otherwise, this flow chart is unchanged.

- Details of Sampling for Pharmacokinetics and Pharmacodynamics for Part A-2. This flow chart is entirely new.

- Part B: 2 Week Schedule. This flow chart is now specific for patients who are following an every 2 week dosing schedule. This flow chart is unchanged with the following exceptions:

    - Footnote 7: See Appendix 6.1 for list of laboratory tests. Routine laboratory tests (e.g., CBC with differential; comprehensive serum chemistry panel; urinalysis) will be performed by the local study site laboratory or their contract laboratory. Following Week 24, urinalysis should be performed every 8 weeks. *CBC, serum chemistry and urinalysis may be collected up to 48 hours prior to any Cycle "X", Day 1 dosing.*

    - Footnote 19: Tumor imaging (either CT or MRI, with strong preference for CT; lung x-ray) will be performed within 30 days prior to enrollment. The same imaging technique has to be used in a patient throughout the study. After first documentation of response or progression, repeat imaging is required approximately 4 weeks later for confirmation, as per immune related response criteria (irRC) guidelines (see Appendix 6.5). *Week 16 needs to be performed if Week 12 imaging indicates stable disease (SD),* a response (CR or PR) or progressive disease (see Section 2.4.1). Response status will be assessed by the study site and by a central imaging vendor. The process for collection of CT images and transmission to the central vendor for purpose of central response review is described in the procedures manual. Following Week 24, tumor imaging will be performed approximately every 12 weeks (or whenever clinically indicated) while the patient remains on study therapy.

- Part B: 3 Week Schedule. This flow chart is entirely new.

- Part C: 3 Week Schedule. This flow chart is entirely new.

- Part B and C Follow-up. This flow chart in now specific for Part B and Part C. This includes survival follow up every 60 days (phone call) after FU 2 visit for 2 years (addition of footnote 11 and 12) for Part C.

2.1.1 Primary Objectives

1) To evaluate and characterize the tolerability and safety profile of single agent MK-3475 in adult patients with unresectable advanced carcinoma *(including NSCLC or* MEL*)*~~, and to determine a RP2D for subsequent testing~~.

2) To evaluate anti-tumor activity of MK-3475 in MEL *and NSCLC*.

Hypothesis: Single agent MK-3475 will show *a clinically meaningful response rate (RR) or disease-control-rate (DCR)* ~~a response rate (RR) and/or disease control rate (DCR)~~ in *ipilimumab-naïve* MEL *patients, or a clinically meaningful response rate (RR) in MEL patients previously treated with ipilimumab or in NSCLC patients* that merits further investigation (for details, see Section 3.5, Statistical Analysis Plan).

2.1.2 Secondary Objectives

5) To evaluate response duration, progression-free survival and overall survival of NSCLC patients who are treated with MK-3475.

2.2 Patient Inclusion Criteria

Inclusion criteria 1 and 2 have been combined. Consequently, Inclusion Criteria 3 through 9 have been renumbered to Inclusion Criteria 2 through 8 respectively. Inclusion Criteria 2 and 6 are identified with their new numbers in the current amendment. These were Inclusion Criteria 3 and 7 in the previous amendment.

1) *Patient meets the following corresponding requirements for the part of the study they will enroll into:*

In Part A of the study, patients must have a histological or cytological diagnosis of MEL or any type of carcinoma, progressive metastatic disease, or progressive locally advanced disease not amenable to local therapy:

- Please note: Tumor types of primary interest in Part A include but are not limited to malignant MEL, RCC, hepatocellular carcinoma, non-small cell lung cancer, gastric carcinoma, ovarian carcinoma and colorectal carcinoma.

- Patients must have failed established standard medical anti-cancer therapies for a given tumor type or have been intolerant to such therapy, or in the opinion of the Investigator have been considered ineligible for a particular form of standard therapy on medical grounds.

In Part B of the study, patients must have a histological *or cytological* diagnosis of MEL with progressive locally advanced or metastatic disease that is not amenable to definitive local therapy with curative intent.

- Patients naive to ipilimumab may not have received more than 2 prior systemic treatment regimens for treatment of MEL. One of them can be a BRAF inhibitor. *Ipilimumab treated patients may not have received more than 3 prior systemic treatment regimens. One of them can be a BRAF inhibitor.*

- Patients may not have a diagnosis of uveal melanoma.

- After the first 13 patients are enrolled, patients who have had ipilimumab may be enrolled, provided the following requirements are met:
    - Full resolution of ipilimumab related adverse effects (including immune-related adverse effects) and no treatment for these adverse events (AEs) for at least 4 weeks prior to the time of enrollment.
    - Minimum of 12 weeks from the first dose of ipilimumab and >6 weeks from the last dose.
        - No history of severe immune related adverse effects from ipilimumab (CTCAE Grade 4; CTCAE Grade 3 requiring treatment >4 weeks).
        - Unequivocal PD ~~during or after treatment with~~ *within 6 months of the first dose of* ipilimumab

In Part C of the study, patients must have a histologically-confirmed or cytologically-confirmed diagnosis of non-small cell lung cancer.

- *Patient has experienced progression of locally advanced or metastatic NSCLC after two prior systemic antineoplastic regimens (Adjuvant therapy will count as a regimen if administered within 1 year before the relapse).*
- *Patient has an estimated life expectancy of at least 12 weeks.*

2) In Part B *and C* of the study, patients must have measurable disease as defined per irRC (Appendix 6.5).

6) Patient (Parts A, ~~and~~ B, *and C*) has voluntarily agreed to participate by giving written informed consent. For Parts B *and C*, patient has voluntarily agreed to a fresh biopsy of tumor (that can be biopsied based on investigator's assessment) and to providing the acquired tissue for biomarker analysis

2.3 Patient Exclusion Criteria

1) Sub bullet:

- Patient who has had ipilimumab therapy may be enrolled in Part B *or Part C* of the study (after 13 ipilimumab naïve patients are enrolled) if time from last treatment is >6 weeks and the other requirements specified in Inclusion Criterion *1*) are met.

3) Patient is expected to require any other form of antineoplastic therapy while on study *(including maintenance therapy with another agent for NSCLC).*

Exclusion Criteria 5 has been deleted and has been replaced with the following text.

5) ~~Patient is on chronic systemic anti-coagulation treatment with warfarin (low molecular weight heparin or low dose aspirin are permitted).~~

Patient has a history of acute diverticulitis, intra-abdominal abscess, GI obstruction, abdominal carcinomatosis which are known risks factors for bowel perforation.

6) Sub bullet:

- Note: The time requirement for no evidence of disease for 5 years does not apply to the tumor for which a patient is enrolled in the study. The time requirement also does not apply to patients who underwent successful definitive resection of basal cell carcinoma of the skin, superficial bladder cancer, *squamous cell carcinoma of the skin*, or in situ cervical cancer

10) Patient had prior therapy with an anti-PD-1 antibody or an antibody targeting other immuno-regulatory receptors or mechanisms (with exception of ipilimumab in study Part B *and Part C*).

2.4.1 Summary of Study Design

This is an open-label, non-randomized, Phase I study in patients with locally advanced or metastatic MEL, *NSCLC,* or carcinoma. The study has *3* parts.

Part A *(including Part A-1 and A-2)*

Part A *dose escalation* will use a 3+3 design and will enroll cohorts of 3-6 patients with MEL or any type of carcinoma sequentially at escalating doses of 1.0, 3.0 and 10 mg/kg. Dose escalation will continue until identification of a MTD, up to a maximum dose of 10 mg/kg. *Following completion of the dose escalation, additional patients will be enrolled in Part A-1 and Part A-2 as described in Section 1.6 to further define the PK and pharmacodynamic characteristics.*

Radiological assessment of tumor response status should be performed approximately every 2 months for the first 12 months of treatment and approximately every 3 months thereafter. (If considered more appropriate by the investigator, disease monitoring by radiological imaging can continue at 2-month intervals beyond the first 12 months). *The same imaging technique as used at baseline has to be used throughout the study*.

Part B

Part B will only enroll patients with MEL. MK-3475 will be administered at *2 mg/kg and 10 mg/kg*. The dosing interval to be used in Part B *for patients who consent under protocol amendment 001-02 will be repeated Q2W. These patients will continue Q2W dosing until they discontinue study therapy. For patients consented under protocol*

amendment 001-03 or following approval of the administrative memo dated 06-Jan-2012, dosing will be Q3W. Study treatment will continue until disease progression, unacceptable toxicity, or the investigator considers it in the best interest of a patient to discontinue study therapy.

It is expected that Part B will enroll approximately *116* patients, including *76* ipilimumab-naïve patients: *approximately 61 patients at 10 mg/kg and 15 patients at 2 mg/kg. Along with approximately 40 patients who had previously received ipilimumab (at 10 mg/kg).* The first 13 patients will be required to be ipilimumab-naive.

After radiological tumor assessment at screening, the first radiological assessment of tumor response status will be performed at Week 12 (± 1 week), unless there is clinical indication warranting earlier radiologic imaging. *The same imaging technique as used at baseline has to be used throughout the study.*

Part C

Part C will only enroll patients with NSCLC who have experienced progression after two prior systemic anti-tumor regimens. MK-3475 will be administered at a preliminary RP2D, 10 mg/kg. Dosing in Part C will be repeated every 3 weeks. Study treatment will continue until disease progression, unacceptable toxicity, or the investigator considering it in the best interest of a patient to discontinue study therapy.

Patients will be monitored regularly for safety, efficacy and anti-MK-3475 antibodies throughout the study, as per the guidelines in Section 1.7. Fresh tumor biopsies for biomarker analysis are mandatory prior to the first dose at baseline. If accessible, archived tumor tissue should be also collected for biomarker analysis. Tumor biopsies require prior written patient consent.

It is expected that Part C will enroll approximately 35 patients at 10 mg/kg.

<u>Radiological Tumor Assessment in Part C</u>

With the exception of imaging timelines (described below), the response criteria and patient management will follow the described principles and guidelines as per Part B.

For patients in Part C, following radiological tumor assessment at screening, the first radiological assessment of tumor response status will be performed at Week 9 (± 1 week), unless there is clinical indication warranting earlier radiologic imaging. The same imaging technique as used at baseline has to be used throughout the study.

If imaging at 9 weeks shows stable disease (SD), treatment will be continued and the next imaging studies will be conducted approximately at Week 18.

If imaging at 9 weeks shows a complete response (CR) or partial response (PR), tumor imaging will be repeated at approximately Week 13 to confirm response. Alternatively,

patients may wait until the beginning of Week 18 for repeat imaging. Following Week 18, tumor imaging will be conducted approximately every 9 weeks subsequently.

In patients who have radiological PD at Week 9, it is at the discretion of the investigator to keep a patient on study until repeat imaging 4 weeks later or rather take a patient off study. This decision will be based on clinical judgment of a patient's overall clinical condition, including performance status, clinical symptoms, and laboratory data.

2.4.2 Definition of Dose-Limiting Toxicities

Heading added: ***Replacement of Patients in the DLT Period***

2.4.3 Treatment Plan

The following table (Table 2-3) displays the distribution of patients, along with the respective dose and dosing interval.

Table 2-3
Patient Distribution

	Amendment 001-02	*Amendment 001-03 (new)*	*Total N*
Part A Dose Escalation	*N=10*[1]		*28 solid tumor*
Part A-1	*N=6*[1]		
Part A-2		*N=12 (Q3W)*	
Part B (MEL)	***Ipilimumab naïve*** *at 10 mg/kg (Q2W)*[2] *N=46*	***Ipilumumab naïve*** *at 10 mg/kg (Q3W) N=15*	*61*
	Ipilimumab treated *at 10 mg/kg (Q2W)*[2] *N=20*	***Ipilimumab treated*** *at 10 mg/kg (Q3W) N=20*	*40*
		Ipilimumab naïve *at 2 mg/kg (Q3W) N=15*	*15*
Part C (NSCLC)		*10 mg/kg (Q3W) N=35*	*35*

1 The dosing interval between Cycle 1 and Cycle 2 is 28 days, Cycle 2 and beyond will be repeated every 14 days
2 Patients in Part B are dosed Q2W. Following approval of Amendment 001-03 or following approval of the administrative memo dated 06-Jan-2012, new patients will be dosed Q3W.

Dose escalation in individual patients will not be permitted in this study, *except as indicated for patients enrolled in Part A-2. In addition, for detailed guidelines for dose modifications and treatment holidays, see Section 3.2.5.4.9 and 3.2.5.4.10 respectively.*

Continuation of study therapy beyond 2 years will be contingent on the continued availability of MK-3475 drug product.

2.5 List of Efficacy/Pharmacokinetic/Immunogenicity Measurements

The Study Flow Chart (Section 1.7) provides specific details on collection time points. Details of collection procedures are found in the Procedures Manual for this study.

Part A and B *and C*

- PK measurements (for detailed PK profiling in Part A, and for assessment of C_{trough} and terminal half-life in Part B *and C*)

Part B *and C*

The following evaluations will be performed up to Week 12 *(Q2W) and Week 18 (Q3W):*

The following evaluations will be performed up to Week 8 *(Q2W) and Week 9 (Q3W)*:

2.7 Statistical Analysis Plan Summary

The primary purpose of this study is to investigate the safety, tolerability *and anti-tumor activity* of MK-3475 administered intravenously to patients *with progressive locally advanced or metastatic carcinomas, melanoma and non-small cell lung cancer*.

Efficacy Assessment

For Part A, patients' best tumor response along with tumor type and other baseline characteristics will be listed. In Part B, overall response rate (RR) and disease control rate (DCR) will be used as *the* primary endpoints for efficacy assessment *of the ipilimumab-naïve patients*. A 95% confidence interval along with a one-sided p-value for testing the null hypothesis based on the binomial distribution will be provided for both primary endpoints. The trial is considered to have reached the efficacy objective *in this population* if the two corresponding p-values for testing the null hypothesis are less than 5% OR either one is less than 2.5% based on the Hochberg procedure [19]. *RR will be the primary endpoint for efficacy assessment of the patients previously treated with ipilimumab (Part B) and the NSCLC patients (Part C). A 95% confidence interval for RR will be provided for each population.*

In addition, Kaplan-Meier plots and descriptive statistics *of* progression-free-survival (PFS) and overall survival (OS) *will be provided for all three populations (ipilimumab-naïve patients, patients previously treated with ipilimumab and NSCLC patients).* Descriptive statistics will also be provided for analysis of response duration.

Sample Size Calculations

With *61* ipilimumab-naïve patients *treated at RP2D,* the study has approximately 97% power to detect an effect size of RR=25% or DCR=50% under the null hypothesis of RR=10% and DRC=30%, or *>99*% power to detect an effect size of RR=30% or DCR=55%, at a type I error rate of 5% (one-sided) based on the Hochberg procedure. *For the subgroup of patients on same dosing schedule (Q2W or Q3W), the corresponding powers to the two effect sizes are respectively 87% and 97% when the sample size is 40. 76% and 91% when the sample size is 30, and 44% and 62% when the sample size is 15.*

With 40 patients previously treated with ipilimumab, treated at RP2D, the study has approximately 92%/98% power to rule out a ≤5% RR (null hypothesis) when the true RR is 20%/25% at the 5% type I error rate (one-sided). For the subgroup of patients on the Q3W dosing schedule, the corresponding powers are 75%/90% when sample size is 30 and 59%/78% when sample size is 20.

With 35 NSCLC patients treated at RP2D, the study has approximately 80% power to rule out a ≤9% RR (null hypothesis) when the true RR is 22% at the 10% type I error rate (one-sided).

If 42-48 ipilimumab-naïve patients in Part B have both post-treatment disease assessments and valid evaluation of baseline PD-L1 expression levels in fresh tumor biopsies, the study has approximately 90% power to detect a one-fold difference in concordance (i.e., odds of concordance relative to discordance = 2) using Kendall's tau at a type I error rate of 2.5% (one-sided).

With 21-28 patients (in either ipilimumab-treated population of Part B or in NSCLC population of Part C), Kendall's tau has 90% power to detect a 1.5 to 2-fold difference at a type I error rate of 2.5% (one-sided).

3.2.5.1.2 Consent to Tumor Biopsy

Part C will also investigate biomarkers in tumor tissue that may be able to identify which NSCLC patients have a high probability to benefit from treatment with MK-3475 and which not. Thus a fresh tumor biopsy before start of study treatment is a mandatory requirement for participation in Part C. Patients must give written consent before tumor biopsies. The most likely candidate biomarker (PD-L1) is most likely to be expressed later in the patient's disease course, thus a fresh sample will be needed to correlate with objective response or clinical benefit, rather than use an archival tissue block greater than two months old from the time of signing informed consent.

3.2.5.4.5 Electrocardiogram (ECG)

In Part A, a 12-lead ECG should be performed at Screening, at the Safety Follow-up Visit, and during study at the time points described in Section 1.7 (Study Flow Chart). In Part B, a 12-lead ECG should be performed at Screening, Cycle 1, and at the Safety

Follow-up Visit. *In Part C, a 12-lead ECG should be performed at Screening, Cycle 1, and at the Safety Follow-up Visit.*

3.2.5.4.6 Guidelines for Study Drug Administration

MK-3475 will be administered as a 30 minute IV infusion*, with a window of -5 and +10 minutes (except as indicated in Part A-2).*

Part A consists of a dose escalation followed by additional analysis of PK and PD characteristics. Part A *will begin with a dose escalation where* 3 dose levels of MK-3475 will be evaluated: 1 mg/kg, 3 mg/kg and 10 mg/kg. To ascertain proper PK sampling and analysis, the interval between the first and second dose in Part A will be 28 days. In subsequent cycles, the dosing interval will be 14 days. *Part A-1 and A-2 will enroll additional patients to explore the PK and PD characteristics as described in Sections 1.5 and 1.6. Patients in Part A-2 receiving less than 1.0 mg/kg of MK-3475 will have study drug administered via IV push.*

Specific instructions for dose calculation, reconstitution, preparation of the infusion fluid, and administration of MK-3475 as both an IV push and infusion are provided in the Procedures Manual.

Patients in Part B will receive MK-3475 at the preliminary RP2D*(s)* determined in Part A. *The dosing interval to be used in Part B for patients who consent under protocol amendment 001-02 will be repeated Q2W. These patients will continue Q2W dosing until they discontinue study therapy. For patients consented under protocol amendment 001-03 or following approval of the administrative memo dated 06-Jan-2012, dosing will be Q3W.*

Patients in Part C will receive MK-3475 at a preliminary RP2D, 10 mg/kg. The dosing interval will be every 3 weeks.

3.2.5.4.8 Preliminary RP2D for Use in Part B *and C*

The dose*(s)* to be used in Part B of the study will be determined based on the data from Part A. The parameters considered for selection of *the* preliminary RP2D(s) will include safety profile, PK, pharmacodynamics, *and anti-tumor efficacy*. Additional patients *(approximately 18) will* be enrolled *in P*art A *since more* robust PK characterization of MK-3475 is deemed warranted *as described in Sections 3.1.2 and 3.1.3. Enrollment of these patients and the subsequent dosing is described in Section 1.6.*

3.2.5.4.9 Guidelines for Dose Modification

Bullet:

- Inability to reduce corticosteroid dose for immune-related adverse reactions to *<10* mg prednisone or equivalent per day.

Study therapy will be withheld for the following adverse reactions:

- Grade *3* non-hematological toxicity, with the exception of the adverse reactions listed under requirement of permanent discontinuation of study therapy.

In case toxicity does not resolve to Grade 0-1 within *6* weeks after last administration of study drug, study therapy will be discontinued. In patients who continue on study therapy after experiencing such toxicity, the dosing interval in subsequent cycles will be increased by 1 week (e.g., to 3 weeks in patients who were on an every 2 week schedule).

3.2.5.4.11 Supportive Care Guidelines

Sub-Bullet:

- In patients with moderate enterocolitis, MK-3475 should be withheld and anti-diarrheal treatment should be started. If symptoms are persistent for more than one week, systemic corticosteroids should be initiated *(e.g.,* 0.5 mg/kg/day of prednisone or equivalent*)*. When symptoms improve to Grade 1 or less, corticosteroid tape should be started and continued over at least 1 month. Regarding guidelines for continuing treatment with MK-3475, see Section 3.2.5.4.9

Immune-related adverse events: Patients who develop *a G2 or higher* irAE (e.g., colitis, skin rash, hepatitis, uveitis, hypo- or hyperthyroidism, hypophysitis, or any other), should be discussed immediately with the SPONSOR. Depending on the type and severity of an irAE, oral or intravenous treatment with a corticosteroid should be considered, in addition to appropriate symptomatic treatment of a given condition.

3.2.5.1.13 Safety Follow-up Visit

After a patient is discontinued from study therapy (in Part A and Part B *and Part C*), a mandatory Safety Follow-Up Visit should be performed approximately 30 days after the last infusion of study medication. Procedures and assessments performed at the Safety Follow-Up Visit and beyond should follow the respective guidelines described in the Study Flow Chart (Section 1.7) for Part A or Part B *and C* as appropriate

3.2.5.4.14 Duration of Follow-up

In all patients in Part A, every effort should be made to collect blood samples for PK every 4-8 weeks and antibodies to MK-3475 approximately every 2 months after last drug administration, for a total period of 24 weeks. In Part B *and C*, every effort should be made to collect blood samples for PK and antibodies to MK-3475 approximately every 12 weeks, for a total period of 24 weeks after last drug administration. The first collection of blood samples can be performed at the time of the mandatory Safety Follow-Up Visit.

In Part B patients who discontinued study therapy without documented disease progression, monitoring of their disease status by radiologic imaging should continue following the guidelines described in the Study Flow Chart (Section 1.7; Part B *and C* Follow-Up). Disease monitoring should continue (1) for approximately 6 months without disease progression, (2) until start of a new anti-cancer treatment, (3) until documented disease progression, or (4) until death, whichever occurs first.

In Part C patients who discontinued study therapy without documented disease progression, monitoring of their disease status by radiologic imaging should continue following the guidelines described in the Study Flow Chart (Section 1.7; Part B and C Follow-Up). Disease monitoring should continue (1) for approximately 6 months without disease progression, (2) until start of a new anti-cancer treatment, (3) until documented disease progression, or (4) until death, whichever occurs first.

Patients will be followed long-term for survival, as described in the Study Flow Chart (Section 1.7, Part B and C: Follow Up).

3.3.1.1 Response Criteria

In Part C, the irRC will also be applied as the primary measure for assessment of tumor response and as basis for all protocol guidelines related to disease status (e.g., discontinuation of study therapy). The irRC system is specifically described in the IIOM and in Appendix 6.5. RECIST 1.1 will be applied as a secondary measure. In addition, evaluation of volumetric tumor response will be performed by a central imaging vendor (see IIOM for details).

3.3.1.2 Efficacy Endpoints

Part B

In Part B, two *co*-primary endpoints will be used to determine anti-tumor activity in *ipilimumab-naïve* MEL *patients*: response rate (RR) and disease control rate (DCR). RR will include patients with CR or PR. DCR will include patients with CR, PR and stable disease (SD). RR and DCR will be based on the best tumor response documented in a patient over the entire course of the study. In addition RR and DCR will be assessed at approximately Weeks 12 and 24.

The primary endpoint for MEL patients previously treated with ipilimumab is RR. All other endpoints as defined above will serve as secondary endpoints.

Part C

The primary endpoint for NSCLC patients used to determine anti-tumor activity is RR. RR will include patients with CR or PR.

Secondary efficacy endpoints determined in Part C will include duration of response, PFS and OS. Duration of response will be measured from first documentation response

to first documentation of disease progression. PFS will be measured from start of treatment to documentation of definitive disease progression as defined by irRC or death due to any cause, whichever occurs first. Survival will be measured from start of treatment to death due to any cause.

3.3.1.3 Radiographic Assessment

In Part A and Part B *and Part C* patients, baseline tumor imaging (CT or MRI, with a preference for CT) examinations must be performed within 30 days before enrollment. The same imaging technique as used at baseline has to be used throughout the study.

Part C

With the exception of imaging timelines (described below), the response criteria and patient management will follow the described principles and guidelines as per Part B.

For patients in Part C, following radiological tumor assessment at screening, the first radiological assessment of tumor response status will be performed at Week 9 (± 1 week), unless there is clinical indication warranting earlier radiologic imaging.

If imaging at 9 weeks shows stable disease (SD) as per irRC, treatment will be continued and the next imaging studies will be conducted approximately at Week 18.

If imaging at 9 weeks shows a complete response (CR) or partial response (PR), tumor imaging will be repeated at approximately Week 13 to confirm response. Alternatively, patients may wait until the beginning of Week 18 for repeat imaging. Following Week 18, tumor imaging will be conducted approximately every 9 weeks subsequently.

3.3.2 Pharmacokinetic Measurements

Part A

PK analysis in Part A will include but is not limited to $AUC_{0\text{-}28day}$, C_{max} and T_{max}, C_{trough} t½, Cl and Vd.

The time points for PK blood sampling are described in Section 1.7 (Study Flow Charts: Details of Sampling for Pharmacokinetics and Pharmacodynamics *for Part A and A-1 and Details of Sampling for Pharmacokinetics and Pharmacodynamics for Part A-2*).

Part B

In Part B, PK profile of MK-3475 will be further characterized using a population modeling approach.

The time points for PK blood sampling are described in Section 1.7 (Part B Study Flow Charts *for 2 weeks and 3 weeks*).

Part C

In Part C, PK profile of MK-3475 will also be further characterized using a population modeling approach.

The time points for PK blood sampling are described in Section 1.7 (Part C Study Flow Chart).

3.3.3 Pharmacodynamic Measurements

Pharmacodynamic measurements will only be performed in Part A of the study. Details on collection of blood samples, processing, storage, and shipping details are provided in the Procedures Manual. The time points for pharmacodynamic blood sampling are described in Section 1.7 (Study Flow Charts: Details of Sampling for Pharmacokinetics and Pharmacodynamics *for Parts A and A-1, and Details of Sampling for Pharmacokinetics and Pharmacodynamics for Part A-2*).

3.3.4 Biomarkers

The primary biomarker objective is to assess the relationship between PD-L1 expression levels and anti-tumor activity of MK 3475 *in patients* with MEL and *NSCLC*.

The study of single dose MDX-1106 published data from nine patients who had tissue biopsies from their tumors that were tested for expression of PD-L1 by immunohistochemistry. Three of four patients who demonstrated membranous staining for PD-L1 had regression of their tumor burden. The fourth patient that demonstrated membranous staining for PD-L1 had been treated at the lowest tested dose in the protocol (0.3 mg/kg) and did not experience regression of tumor burden. The remaining five patients who provided tumor tissue for testing did not express PD-L1 and did not experience any clinical response. The authors of this paper believed that a potentially significant correlation between membranous PD-L1 staining on tumor cells and the likelihood of tumor regression following treatment with MDX-1106 existed with a two-sided p-value of 0.0476 by Fischer's exact test [17].

Therefore, PD-L1 expression levels will be measured in MEL *and NSCLC* tumor tissues by immunohistochemistry (IHC) performed on tissue micro-arrays (TMAs). The assay will utilize fluorescence labeling and computerized detection/quantification system to provide a more sensitive and continuous detection range and single numerical expression index (i.e., combination of percent positivity and expression activity) rather than conventional IHC categorization.

3.4.8 Events of Clinical Interest

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 Administrative Binder, or equivalent).*

3.5.2 Hypotheses/Estimation

The following table (Table 3-3) provides the target RR and DCR of interest for the ipilimumab-naïve population. The null hypothesis is derived from the published Phase III data on single agent ipilimumab [71], and the alternative hypothesis is derived from the MDX-1106 data as reported at the 2010 American Society of Clinical Oncology (ASCO) meeting [74]. To properly reflect the preliminary nature of the MDX-1106 data, two effect sizes are considered for the alternative hypothesis (intermediate and high), with the high effect size representing the data as reported and the intermediate effect size representing a slightly lower efficacy size that is still considered of clinical interest.

There is no historical data to benchmark patients previously treated with ipilimumab. The null hypothesis on RR is chosen to be ≤5%, and the alternative hypothesis is chosen to be 20%/25%. For NSCLC patients, the null hypothesis on RR is chosen to be ≤9%, and the alternative hypothesis is chosen to be 22%.

Table 3-3

Target Response Rate (RR) and Disease Control Rate (DCR) of Interest *in Ipilimumab-naïve Population*

An important secondary objective of study Part B *and Part C* is to investigate the correlation between various candidate biomarkers and anti-tumor activity of MK-3475. The primary biomarker hypothesis to be tested in the study is that expression of PD-L1 in tumor tissue at baseline *is* concordant with anti-tumor activity, assessed as maximum total reduction (%) in tumor volume produced by MK-3475.

3.5.3.1 Efficacy Endpoints

RR and DCR will serve as co-primary efficacy endpoints *for the ipilimumab-naïve population* in Part B of the study. This means that either RR or DCR needs to achieve the target effect size for the study to be considered positive. The recently published immune-related response criteria (irRC) will be applied as primary measure for assessment of tumor response [18]. RR and DCR will be also assessed based on RECIST 1.1. Interim analyses will be based on RR and DCR at week 12. Confirmation is required for final analysis of RR, but not for the interim analyses.

Secondary efficacy endpoints *for the ipilimumab-naïve population* determined in Part B will include duration of response, progression-free survival (PFS) and overall survival (OS). Response duration will be only determined for confirmed responses and is defined as the time from first documentation of response to first documentation of disease progression. PFS will be measured from start of treatment to documentation of definitive disease progression as defined by irRC or death due to any cause, whichever occurs first. OS is defined as time from treatment initiation to death due to any cause.

The primary endpoint for both MEL patients previously treated with ipilimumab and NSCLC patients is RR. All other endpoints as defined above will serve as secondary endpoints.

3.5.3.4 Predictive Biomarker Endpoints

The primary candidate biomarker to be investigated in study Part B *and Part C* is PD-L1 expression levels in tumor tissue at baseline, which will be assessed by IHC. Other candidate biomarkers which will be investigated include expression of PD-L2 and PD-1, RNA signature profiles, and quantitative RNA expression of candidate genes of interest, including PD-L1.

3.5.4.1 Efficacy Analysis

The primary efficacy analyses will be based on the Full Analysis Set (FAS) population *for each of the three sub-populations (ipilimumab-naïve patients in Part B, patients previously treated with ipilimumab in Part B and NSCLC patients in Part C) treated at RP2D.* Patients with measurable disease at baseline who received at least one dose of study treatment will be included in the FAS population.

3.5.4.2 Safety Analysis

The All Patients as Treated (APaT) population will be used for the analysis of safety data in this study. The APaT population consists of all patients who received at least 1 dose of study treatment in Part A, Part B *and Part C*.

3.5.4.4 Predictive Biomarker Analyses

The primary predictive biomarker analysis is based on a subset of the FAS population in Part B *and Part C* that includes patients with both a valid PD-L1 expression measurement and at least one disease assessment post-treatment. A supportive analysis is based on a subset of the FAS population that includes patients with a valid PD-L1 expression measurement, irrespective of the availability of post-treatment disease assessments. In this analysis, those without post-treatment disease assessments will be imputed with the worst outcome in tumor response (see 3.5.5.4 for details).

3.5.5.1 Efficacy Analysis

In Part B, overall response rate (RR) and disease control rate (DCR) will be used as co-primary endpoints for efficacy assessment of the ipilimumab-naïve patients. A 95% confidence interval along with a one-sided p-value for testing the null hypothesis based on the binomial distribution will be provided for each for the two co-primary endpoints: overall RR and overall DCR. Similar analyses will be provided for interim analyses of RR and DCR at week 12. Kaplan-Meier plots and descriptive statistics will be provided for progression-free-survival (PFS) and overall survival (OS). Descriptive statistics will also be provided for analysis of response duration. Exploratory analyses will be conducted to compare the PFS rate at 6-month and OS rate at 1-year with historical control as well as with the recent ipilimumab data adjusted with baseline factors such as ECOG [75].

RR will be the primary endpoint for efficacy assessment of the patients previously treated with ipilimumab (Part B) and the NSCLC patients (Part C). A 95% confidence interval for RR will be provided for each population. Kaplan-Meier plots, and descriptive statistics of DCR, response duration, progression-free-survival (PFS) and overall survival (OS) will also be provided.

3.5.5.4 Predictive Biomarker Analysis

Kendall's tau statistics will be used for the primary predictive biomarker *analyses* [20]. The test statistics along with a one-sided p-value will be provided for testing the concordance between maximum total tumor volume reduction (%) produced by MK-3475 and PD-L1 expression levels in tumor tissue. Kendall's tau statistics is rank based. For the supportive analysis, those without a post-treatment disease assessment (presumably mainly due to discontinuation before week 12) will be assigned a lower rank (equivalent to less tumor reduction) than those with a post-treatment disease assessment. They will further be ranked by category of reasons for discontinuation (death, disease progression and other reasons) in ascending order, and among each category they will be ranked by time to discontinuation, the earlier the lower.

3.5.6 Multiplicity

The predictive biomarker hypothesis on PD-L1 will be formally tested at a type I error rate of 2.5% (one-sided) *separately for Part B and Part C*, irrespective of the outcome from efficacy analyses. Once the null hypothesis is rejected, a step-down procedure may be applied to the testing of other biomarker hypotheses prospectively specified before the end of the study (in a separate document). While additional exploratory analyses will be conducted to evaluate alternative predictive biomarkers, there is no multiplicity control of such analyses and no formal conclusion can be made.

The efficacy hypothesis is tested at 5% (one-sided) for both the ipilimumab-naïve population and the ipilimumab-treated population, and at 10% (one-sided) for the NSCLC population. Altogether, there is an approximately 20% (i.e., 5%+5%+10%)

chance that the efficacy outcome is positive in one of the three study populations under the null hypotheses. In absence of a control arm, any positive outcome (and for the same matter a negative outcome) has to be interpreted with caution.

3.5.7 Sample Size and Power Calculations

With 61 ipilimumab-naïve patients treated at RP2D, the study has approximately 97% power to detect an effect size of RR=25% or DCR=50% under the null hypothesis of RR=10% and DRC=30%, or >99% power to detect an effect size of RR=30% or DCR=55%, at a type I error rate of 5% (one-sided) based on the Hochberg procedure. For the subgroup of patients on same dosing schedule (Q2W or Q3W), the corresponding powers to the two effect sizes are respectively 87% and 97% when the sample size is 40 76% and 91% when the sample size is 30, and 44% and 62% when the sample size is 15.

With 40 patients previously treated with ipilimumab treated at RP2D, the study has approximately 92%/98% power to rule out a ≤5% RR when the true RR is 20%/25% at the 5% type I error rate (one-sided). For the subgroup of patients on the Q3W dosing schedule, the corresponding powers are 75%/90% when sample size is 30 and 59%/78% when sample size is 20.

With 35 NSCLC patients treated at RP2D, the study has approximately 80% power to rule out a ≤9% RR when the true RR is 22% at the 10% type I error rate (one-sided).

Patients may discontinue the study before week 12 just as in an ipilimumab study [72], and not all the remaining patients will have valid data for analysis. Assuming that 42-48 ipilimumab-naïve patients have both post-treatment disease assessments and valid baseline PD-L1 expressions in fresh tumor biopsies, the study has approximately 90% power to detect a one-fold difference in concordance (i.e., odds of concordance relative to discordance = 2) using Kendall's tau at a type I error rate of 2.5% (one-sided). With 21-28 patients (in either ipilimumab-treated population of Part B or in NSCLC population of Part C), Kendall's tau has 90% power to detect a 1.5 to 2-fold difference at a type I error rate of 2.5% (one-sided).

3.5.8 Subgroup Analyses and Effect of Baseline Factors

In assessment of anti-tumor activity in ipilimumab population, patients will be analyzed by treatment history with ipilimumab and by dose level and dosing interval (Q2W or Q3W). Totality of data including PK/PD and biomarker data will be reviewed before a decision can be made which population or dose interval merits further investigation.

In assessment of the predictive biomarkers in MEL patients, the ipilimumab-naïve population and the ipilimumab-treated population will be separately analyzed for concordance PD-L1 expression and maximum total reduction (%) in tumor volume produced by MK-3475, using Kendall's tau. The two populations will be combined for analysis if there is no evidence suggesting a difference with regard to concordance between the two. In addition to prior experience with ipilimumab, dosing interval,

gender, age category (above or below median), ECOG performance status (0 or 1) and other appropriate prognostic factors will also be explored. Exploratory analyses will also be conducted to compare DCR and RR between "biomarker positive" and "biomarker negative" populations determined by the cut-off point of PD-L1 expression level.

Similarly, in assessment of the predictive biomarkers in NSCLC patients, gender, age category (above or below median), ECOG performance status (0 or 1) and other appropriate prognostic factors will be explored. Exploratory analyses will also be conducted to compare DCR and RR between "biomarker positive" and "biomarker negative" populations determined by the cut-off point of PD-L1 expression level.

3.5.9 Interim Analyses

The study will have two planned interim analyses *for ipilimumab-naïve patients in Part B. There are no planned interim analyses for patients previously treated with ipilimumab or NSCLC patients.* The primary endpoints in these *interim* analyses *for ipilimumab-naïve patients* are RR and DCR at week 12. There is no intention to stop the trial for efficacy at the first or second interim analysis. The accrual for Part B is expected to be fast. Should it be slower than expected, one additional interim analysis may be added. The decision rules at the interim analyses serve as guidance and are non-binding. In absence of a control arm, outcomes in this single arm study have to be interpreted with caution, both at interim and final analyses.

As a comparison to interim analyses, Table 3.4 presents outcome of interest in the ipilimumab-naïve population at the final analysis based on various hypothetical sample sizes. For N varying from 30 to 45, an observed RR of approximately 20-23% OR a DCR of approximately 44-47% is generally required to cross the efficacy bar for a positive study. If the study objective is not met in the all-comer ipilimumab-naïve population, an exploratory analysis will be conducted in a "biomarker positive" subpopulation determined by the PD-L1 cut-off level. Such an analysis will be only performed if the primary biomarker hypothesis is confirmed, i.e., there will be statistical concordance between PD-L1 expression levels at baseline and maximum total tumor volume reduction (%) produced by MK-3475. A Hochberg procedure with type I error rate of 5% (one-sided) will be applied to assist with the analysis.

Heading "Final Analysis" has been deleted.

3.6.1 Patients and Replacements Information

Clinical supplies will be packaged to support enrollment of approximately ***179*** patients/subjects. Clinical supplies will be packaged according to an allocation schedule generated by the SPONSOR

Product: MK-3475 1
Protocol/Amendment No.: 001-04

SUMMARY OF CHANGES

PRIMARY REASON FOR THIS AMENDMENT:

The primary reason for this amendment is a change following review of the 001-03 protocol amendment by the Food and Drug Administration (FDA). This modification is:

- Change from Grade 3 to Grade 2 drug-related non-hematological toxicities in regards to guidance for dose modification as described below:

Section 3.2.5.4.9 Guidelines for Dose Modification

Amendment 001-03 text:

Study therapy will be withheld for the following adverse reactions:

- Grade 3 non-hematological toxicity, with the exception of the adverse reactions listed under requirement of permanent discontinuation of study therapy
  - Grade 2-3 fatigue does not require the withholding of study therapy

New Text

Study therapy will be withheld for the following adverse reactions:

- *A drug-related* non-hematological toxicity ≥*Grade 2*, with the exception of the adverse reactions listed under requirement of permanent discontinuation of study therapy
  - Grade 2-3 fatigue does not require the withholding of study therapy

OTHER CHANGES INCLUDED IN THE AMENDMENT:

There are no other changes to the protocol.

Product: MK-3475 1
Protocol/Amendment No.: 001-05

SUMMARY OF CHANGES

PRIMARY REASON FOR THIS AMENDMENT:

The primary objectives of this amendment are the increase in sample size of Part B, and addition of Part D and Part E. These changes are primarily encompassed by the following:

Part D: Characterize the safety profile and tolerability of MK-3475 and evaluate the clinical activity of MK-3475 in patients with melanoma at the preliminary doses of 2 mg/kg and 10 mg/kg.

Part E: Characterize the safety profile and tolerability and evaluate the clinical activity of MK-3475 in patients with non-small cell lung cancer in combination with chemotherapy in a first line and second line setting at the preliminary doses of 2 mg/kg and 10 mg/kg, and investigate the correlation of biomarker predictability of tumor reduction in patients treated with combination therapy.

Implementation of these objectives necessitates the following changes to the protocol:

- Addition of 60 ipilimumab-refractory patients with melanoma in Part B.
- Addition of 88 patients with melanoma in Part D including the addition of all Part D-specific procedures.
- Addition of 112 patients with non-small cell lung cancer in Part E including the addition of all Part E-specific procedures.

OTHER CHANGES INCLUDED IN THE AMENDMENT:

Throughout the protocol, procedures have been separately listed for Part A, Part B, Part C, Part D and Part E. Changes specific to the conduct of Part A, B, C, D, and E are listed here. Part D and E text should be reviewed in their entirety throughout the protocol.

In addition, typographical error and inconsistencies were corrected throughout the document and are not listed here. Protocol sections that include changes relevant to Part A, Part B, Part C, Part D and Part E but do not impact study conduct of these Parts are not listed here (e.g., 1.3 Summary of Rationale, 3.1.2 Rationale for This Study, 3.1.3 Rationale for Dose) and should be reviewed in their entirety.

Section 1.2 Indication

For Part B, patients with a histologically or cytologically confirmed diagnosis of MEL with progressive locally advanced or metastatic disease that is not amenable to definitive local therapy with curative intent.

- ~~Note: A diagnosis of MEL which is only based on cytology (e.g., from a fine needle biopsy or a malignant effusion) is not sufficient for eligibility in Part B.~~

For Part D, patients with a histologically or cytologically confirmed diagnosis of MEL with progressive locally advanced or metastatic disease that is not amenable to definitive local therapy with curative intent.

For Part E, patients with a histologically or cytologically confirmed diagnosis of non-small cell lung cancer (NSCLC) with progressive locally advanced or metastatic disease after 1 prior systemic platinum-containing doublet therapy regimen or naïve to systemic treatment.

Section 1.3 Summary of Rationale

Redacted

Section 1.4 Summary of Study Design

This is an open-label, ~~non-randomized~~ Phase I study of intravenous (IV) MK-3475 in patients with progressive locally advanced or metastatic carcinomas, especially MEL or NSCLC. **Part A** of the study will use a traditional 3+3 design for dose escalation. Cohorts of 3-6 patients will be enrolled sequentially at escalating doses of 1~~.0~~, 3~~.0~~ and 10 mg/kg. Dose escalation will continue until identification of MTD, up to a maximum dose of 10 mg/kg. Once the dose escalation is completed, additional patients will be enrolled to more fully characterize the PK profile. In **Part B**, patients with MEL will be enrolled at the preliminary RP2D(s) to characterize the tolerability and safety profile of the dose, and for preliminary evaluation of anti-tumor activity in MEL. In **Part C**,

patients with NSCLC will be enrolled at the preliminary RP2D(s) to characterize the tolerability and safety profile of the dose, and for preliminary evaluation of anti-tumor activity in NSCLC. *In **Part D**, patients with MEL will be enrolled at 2 mg/kg and 10 mg/kg to evaluate the tolerability and safety profile of each dose, and for preliminary evaluation of anti-tumor activity in MEL. In **Part E**, patients with NSCLC will be enrolled at 2 mg/kg and 10 mg/kg to characterize the tolerability and safety profile of MK-3475 in combination with chemotherapy, and for preliminary evaluation of the dose and anti-tumor activity in NSCLC. Part E will also evaluate biomarker predictability of tumor reduction in patients treated with MK-3475 in combination with chemotherapies.*

Section 1.5 Sample

A total of approximately *439* eligible patients will be enrolled in this study, with approximately 28 patients in Part A, approximately *176* patients in Part B, approximately 35 patients in Part C, *approximately 88 patients in Part D, and approximately 112 pts in Part E.*

In Part B, only patients with MEL may be enrolled (metastatic MEL or patients with locally advanced disease and not candidates for surgical resection or a definitive local therapy), and patients must have measurable disease (see Section 2.2 and Appendix 6.5). Part B will enroll approximately 176 patients distributed as described in Table 1-1:

Table 1-1

Patient Distribution in Part B

	10 mg/kg	2 mg/kg
Ipilimumab Naïve	61[1]	15[2]
Ipilimumab Treated	40[1]	0
Ipilimumab Refractory	20[2]	40[2]
1 Includes patients with dosing schedules of Q2W and Q3W. 2 Dosing schedule is Q3W		

Enrollment of patients at 2 mg/kg *who are naïve to ipilimumab* in Part B will begin once all 10 mg/kg patients in Part B are enrolled *up through amendment 04*. All patients enrolled after the approval of current amendment or approval of the administrative memo dated 06-Jan-2012, will be dosed Q3W.

Enrollment of the first 13 patients in Part B will be restricted to ipilimumab-naïve patients (which will serve as basis for the first interim analysis). *The remaining patients will be enrolled without a hold to complete a total of 60 patients (40 ipilimumab-naïve and 20 ipilimumab-treated). With amendment 04, an additional 55 patients (35 ipilimumab-naïve and 20 ipilimumab-treated) will be enrolled. Upon approval of*

amendment 05, the ipilimumab-treated cohort is defined per eligibility criteria in Sections 2.2 and 2.3. Amendment 05 will randomize up to 40 patients at 2 mg/kg and 20 patients at 10 mg/kg who meet the ipilimumab-eligibility criteria (ipilimumab-refractory) as provided in the current amendment in a 2:1 fashion, manually by the Sponsor, based on a computer-generated allocation schedule. These patients are in addition to those enrolled who were previously treated with ipilimumab in amendments 04 and earlier. If a patient is ipilimumab refractory and BRAF V600 mutant, then one of the prior systemic treatment regimes must have been a BRAF and/or MEK inhibitor. Ipilimumab naïve patients are allowed up to 2 prior systemic treatment regimens, one of which may have been prior treatment with a BRAF inhibitor.

In Part D, patients with MEL may be enrolled (metastatic MEL or patients with locally advanced disease and not candidates for surgical resection or a definitive local therapy), and patients must have measurable disease (see Section 2.2 and Appendix 6.5). Part D will enroll approximately 88 patients, randomized 1:1 manually by the Sponsor based on a computer-generated allocation schedule, to either 2 mg/kg or 10 mg/kg. All patients will be dosed Q3W.

Enrollment in Part D will be restricted to ipilimumab-naïve patients who are allowed up to 2 prior systemic treatment regimens, one of which may have been prior treatment with a BRAF inhibitor.

In Part E, 112 patients with NSCLC may be enrolled, and patients must have measurable disease to be enrolled (see Section 2.2 and Appendix 6.5). Eligible patients include progressive metastatic or locally advanced NSCLC who are either treatment naïve or have had 1 prior systemic regimen. All patients will be dosed Q3W.

Patients in Part E will be randomized 1:1, manually by the Sponsor based on a computer-generated allocation schedule, to either 2 or 10 mg/kg of MK-3475 after the investigator chooses the appropriate chemotherapy backbone. There will be 4 different chemotherapies or chemotherapy doublets that may be paired with the 2 doses of MK-3475, allowing for 8 cohorts. Each MK-3475 dose/chemotherapy combination cohort will be limited to 14 patients (28 total patients per chemotherapy). Enrollment will be competitive into each of the 8 cohorts, once each cohort reaches approximately 14 patients the cohort will be closed.

1.6 Dosage/Dosage Form, Route, and Dose Regimen

In Part B, MK-3475 will be administered at the preliminary RP2D(s) as per Section 1.5. For patients who consent under protocol amendment 001-02, dosing will be repeated Q2W. For patients consented under protocol amendments 001-03, *001-04, 001-05*, or following approval of the administrative memo dated 06-Jan-2012, dosing in Part B will be repeated Q3W. Study therapy will continue until disease progression or unacceptable toxicity. Patients who initiate therapy on the 2 week schedule will not switch to the 3 week schedule.

In Part D, MK-3475 will be administered at either 2 or 10 mg/kg. Dosing in Part D will be repeated Q3W. A total of 88 patients will be randomized 1:1, manually by the Sponsor, to either 2 mg/kg or 10 mg/kg MK-3475 using an allocation schedule generated in-house. Once a patient is eligible for treatment, the Sponsor will inform the site of the appropriate dose to administer. Study therapy will continue until disease progression or unacceptable toxicity.

In Part E, MK-3475 will be administered at either 2 or 10 mg/kg in combination with chemotherapy. Dosing of MK-3475, and the corresponding chemotherapy will be repeated Q3W. Determination of either first- or second-line chemotherapy treatment will be based upon the patient's history of previous systemic treatment regimens (0 or 1). A maximum of four cycles of first-line carboplatin/paclitaxel or cisplatin/pemetrexed will be administered along with MK-3475, followed by single agent MK-3475 for subsequent cycles. After completion of the platinum-containing doublet, maintenance therapy with single agent pemetrexed is permitted if the investigator thinks it is appropriate per standard of care (SOC). Determination of dose of MK-3475 will be by random allocation in a 1:1 fashion between 2 mg/kg and 10 mg/kg MK-3475.

Chemotherapies to be delivered according to SOC are: carboplatin/paclitaxel (first line); cisplatin/pemetrexed (first-line); docetaxel (second-line); and pemetrexed (second-line). Determination of which first- or second-line treatment will be investigator choice, limited accordingly by availability of open slots in each cohort.

Listed below are the MK-3475 + chemotherapy treatment options:

- *NSCLC: Treatment naïve (first-line treatment – 56 total patients):*
  - *2 mg/kg MK-3475 + carboplatin/paclitaxel (14 patients)*
  - *10 mg/kg MK-3475 + carboplatin/paclitaxel (14 patients)*
  - *2 mg/kg MK-3475 + cisplatin/pemetrexed (14 patients)*
  - *10 mg/kg MK-3475 + cisplatin/pemetrexed (14 patients)*
- *NSCLC: 1 prior systemic treatment (second-line treatment – 56 total patients):*
  - *2 mg/kg MK-3475 + docetaxel (14 patients)*
  - *10 mg/kg MK-3475 + docetaxel (14 patients)*
  - *2 mg/kg MK-3475 + pemetrexed (14 patients)*
  - *10 mg/kg MK-3475 + pemetrexed (14 patients)*

Section 1.7 Flow Chart

Additional study flow charts have been placed into the protocol. Separate flow charts are provided for the following patient cohorts:

- Part A, Part A-1. This flow chart is unchanged with the following exception:
  - Footnote 6: Vital signs to include temperature, pulse, respiratory rate and blood pressure. *If a patient's baseline weight does not fluctuate by more than 10%, this weight can be used to calculate dose.*
  - Footnote 8: 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. *Study site should contact the patient mid-cycle to assess for potential irAEs.*
  - Footnote 19: Blood collected at predose of Cycle 1 and every month at predose until 6 months of study therapy. Analysis will be performed by a central laboratory. *The last RNA signature profiling sample collected will test for human leukocyte antigen (HLA).*
  - Footnote 25: A fresh biopsy of a tumor lesion is desirable but not mandatory. Written patient consent is required for fresh biopsies. *A baseline biopsy obtained for other purposes (i.e., not a PN001 study procedure), prior to signing consent, can be utilized if obtained within 60 days of first dose of MK-3475 (Cycle 1 Day 1).* Fresh biopsies should be limited to readily accessible tumor lesions (e.g., skin; peripheral lymph nodes; lung, liver or internal lymph node metastases which can be readily accessed using CT guidance). If performed, a tissue cylinder should be obtained that has proper size for histological examination and biomarker analysis (e.g., IHC of PD-1, PD-L1, PD-L2; RNA signature profiling). (See specific guidance for minimum needle gauge in the procedures manual.) When feasible, another tumor biopsy should be taken approximately 2 months after start of study therapy, so tissue characteristics such as biomarkers can be compared to baseline. If feasible, the follow-up biopsy should be ideally taken from the same tumor lesion as the baseline biopsy.
- Part A-2. This flow chart is unchanged with the following exception:
  - Footnote 6: Vital signs to include temperature, pulse, respiratory rate and blood pressure. *If a patient's baseline weight does not fluctuate by more than 10%, this weight can be used to calculate dose.*
  - Footnote 8: 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. *Study*

site should contact the patient mid-cycle (approximately 10 days post-dose) to assess for potential irAEs.

- Footnote 18: Blood collected at predose of Cycle 1 and every month at predose until 6 months of study therapy. Analysis will be performed by a central laboratory. *The last RNA signature profiling sample collected will test for human leukocyte antigen (HLA).*

- Footnote 25: A fresh biopsy of a tumor lesion is desirable but not mandatory. Written patient consent is required for fresh biopsies. *A baseline biopsy obtained for other purposes (i.e., not a PN001 study procedure), prior to signing consent, can be utilized if obtained within 60 days of first dose of MK-3475 (Cycle 1 Day 1).* Fresh biopsies should be limited to readily accessible tumor lesions (e.g., skin; peripheral lymph nodes; lung, liver or internal lymph node metastases which can be readily accessed using CT guidance). If performed, a tissue cylinder should be obtained that has proper size for histological examination and biomarker analysis (e.g., IHC of PD-1, PD-L1, PD-L2; RNA signature profiling). (See specific guidance for minimum needle gauge in the Procedures Manual.) When feasible, another tumor biopsy should be taken approximately 2 months after start of study therapy, so tissue characteristics such as biomarkers can be compared to baseline. If feasible, the follow-up biopsy should be ideally taken from the same tumor lesion as the baseline biopsy.

- Details of Sampling for Pharmacokinetics and Pharmacodynamics for Part A and Part A-1. This flow chart is unchanged.

- Details of Sampling for Pharmacokinetics and Pharmacodynamics for Part A-2. This flow chart is unchanged.

- Part B: 2 Week Schedule. This flow chart is unchanged with the following exceptions:

  - Footnote 4: Vital signs to include temperature, pulse, respiratory rate and blood pressure. *If a patient's baseline weight does not fluctuate by more than 10%, this weight can be used to calculate dose.*

  - Footnote 6: 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. *Study site should contact the patient mid-cycle (approximately 7 days post-dose) to assess for potential irAEs.*

  - Footnote 18: Blood collected at predose of Cycle 1 and before infusion of MK-3475 in Cycles 2, 3, 5 and 7. Analysis will be performed by a

central laboratory. *The last RNA signature profiling sample collected will test for human leukocyte antigen (HLA).*

- Footnote 20: A fresh biopsy of at least one tumor lesion is mandatory at baseline (prior to Cycle 1/Day 1). *A baseline biopsy obtained for other purposes (i.e., not a PN001 study procedure), prior to signing consent, can be utilized if obtained within 60 days of first dose of MK-3475 (Cycle 1 Day 1).* Additional biopsy samples approximately at Week 12, Week 24, and at disease progression are highly desirable. *Further biopsy samples may be obtained at time points other than those specified here if deemed appropriate by the investigator*. When it is feasible, more than one biopsy should be performed at a given time point (e.g., from the same lesion or from different lesions). The tissue sample should have proper size to enable all planned biomarker analyses (e.g., IHC of PD-L1, PD-1, PD-L2; RNA signature profiling). Fine needle aspiration will not be acceptable. The biopsy techniques allowed in the study include tru cut core biopsies or surgical biopsies. Study sites should use the same biopsy techniques in this study as they routinely use for a given tumor lesion/location. Detailed instructions for tissue collection, processing and shipment are provided in the Procedures Manual.

- *Footnote 22: Required at screening for patients without documented BRAF status. Analysis will be performed by a central laboratory.*

- Part B: 3 Week Schedule. This flow chart is unchanged with the following exceptions:

  - Footnote 4: Vital signs to include temperature, pulse, respiratory rate and blood pressure. *If a patient's baseline weight does not fluctuate by more than 10%, this weight can be used to calculate dose.*

  - Footnote 6: 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. *Study site should contact the patient mid-cycle (approximately 10 days post-dose) to assess for potential irAEs.*

  - Footnote 18: Blood collected at predose of Cycle 1 and before infusion of MK-3475 in Cycles 2, 3, 5 and 7. Analysis will be performed by a central laboratory. *The last RNA signature profiling sample collected will test for human leukocyte antigen (HLA).*

  - Footnote 20: A fresh biopsy of at least one tumor lesion is mandatory at baseline (prior to Cycle 1/Day 1). *A baseline biopsy obtained for other purposes (i.e., not a PN001 study procedure), prior to signing consent,*

can be utilized if obtained within 60 days of first dose of MK-3475 (Cycle 1 Day 1). Additional biopsy samples approximately at Week 12, Week 24, and at disease progression are highly desirable. *Further biopsy samples may be obtained at time points other than those specified here if deemed appropriate by the investigator.* When it is feasible, more than one biopsy should be performed at a given time point (e.g., from the same lesion or from different lesions). *Further biopsy samples may be obtained at time points other than those specified here if deemed appropriate by the investigator.* The tissue sample should have proper size to enable all planned biomarker analyses (e.g., IHC of PD-L1, PD-1, PD-L2; RNA signature profiling). Fine needle aspiration will not be acceptable. The biopsy techniques allowed in the study include tru cut core biopsies or surgical biopsies. Study sites should use the same biopsy techniques in this study as they routinely use for a given tumor lesion/location. Detailed instructions for tissue collection, processing and shipment are provided in the Procedures Manual.

- *Footnote 22: Required at screening for patients without documented BRAF status. Analysis will be performed by a central laboratory.*

- Part C: 3 Week Schedule. This flow chart is unchanged with the following exceptions:

  - Footnote 4: Vital signs to include temperature, pulse, respiratory rate and blood pressure. *If a patient's baseline weight does not fluctuate by more than 10%, this weight can be used to calculate dose.*

  - Footnote 6: 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. *Study site should contact the patient mid-cycle (approximately 10 days post dose) to assess for potential irAEs.*

  - Footnote 18: Blood collected at predose of Cycle 1 and before infusion of MK-3475 in Cycles 2, 3, 5 and 7. Analysis will be performed by a central laboratory. *The last RNA signature profiling sample collected will test for human leukocyte antigen (HLA).*

  - Footnote 21: A fresh biopsy of at least one tumor lesion is mandatory at baseline (prior to Cycle 1/Day 1). *A baseline biopsy obtained for other purposes (i.e., not a PN001 study procedure), prior to signing consent, can be utilized if obtained within 60 days of first dose of MK-3475 (Cycle 1 Day 1). Additional biopsy samples approximately at Week 9, Week 18, and at disease progression are highly desirable.* When it is feasible, more than one biopsy should be performed at a given time point (e.g., from the same lesion or from different lesions). *Further biopsy samples may be*

obtained at time points other than those specified here if deemed appropriate by the investigator. The tissue sample should have proper size to enable all planned biomarker analyses (e.g., IHC of PD-L1, PD-1, PD-L2; RNA signature profiling). Fine needle aspiration will not be acceptable. The biopsy techniques allowed in the study include tru cut core biopsies or surgical biopsies. Study sites should use the same biopsy techniques in this study as they routinely use for a given tumor lesion/location. Detailed instructions for tissue collection, processing and shipment are provided in the Procedures Manual.

- Part D: 3 Week Schedule. This flow chart is entirely new
- Part E: 3 Week Schedule. This flow chart is entirely new.
- Details of Sampling for Pharmacokinetics for Patients Receiving 10 mg/kg MK-3475 + Docetaxel in Part E. This flow chart is entirely new.
- Part B, C, D and E Follow-up. This flow chart in now specific for Parts B, C, D and E. This includes survival follow up every 60 days (phone call) after FU 2 visit for 2 years for Part D as well. The following footnote has been changed:
  - ~~Footnote 11: Part C, D, and E patients only~~.

2.1.1 Primary Objectives

Hypothesis: Single agent MK-3475 will show a clinically meaningful response rate (RR) or disease-control-rate (DCR) in ipilimumab-naïve MEL patients, a clinically meaningful RR in MEL patients previously treated with ipilimumab, *a clinically meaningful RR in MEL patients refractory to ipilimumab, and a clinically meaningful RR* in NSCLC patients that merits further investigation (for details, see Section 3.5, Statistical Analysis Plan).

2.2 Patient Inclusion Criteria

1) In Part B of the study, patients must have a histological or cytological diagnosis of MEL with progressive locally advanced or metastatic disease that is not amenable to definitive local therapy with curative intent.
   - Patients naive to ipilimumab may not have received more than 2 prior systemic treatment regimens for treatment of MEL. One of them can be a BRAF inhibitor. ~~Ipilimumab treated patients may not have received more than 3 prior systemic treatment regimens. One of them can be a BRAF inhibitor.~~
   - ~~Patients may not have a diagnosis of uveal melanoma.~~

- After the first 13 patients are enrolled, patients who have had ipilimumab may be enrolled, provided the following requirements are met:
  - Full resolution of ipilimumab related adverse effects (including immune-related adverse effects) and no treatment for these adverse events (AEs) for at least 4 weeks prior to the time of enrollment.
  - Minimum of 12 weeks from the first dose of ipilimumab and >6 weeks from the last dose.
  - No history of severe immune related adverse effects from ipilimumab (CTCAE Grade 4; CTCAE Grade 3 requiring treatment >4 weeks).
  - Unequivocal PD within 6 months of the first dose of ipilimumab.
- *With Amendment 05, patients who have had ipilimumab may be enrolled, provided the following requirements are met (these patients are considered **ipilimumab-refractory**):*
  - *Received at least two doses of ipilimumab.*
  - *Documented disease progression within 24 weeks of the last dose of ipilimumab. Patients who were re-treated with ipilimumab and patients who were on maintenance ipilimumab will be allowed to enter the trial as long as there is documented PD within 24 weeks of the last treatment date (with ipilimumab).*
  - *Progressive disease will be defined as increase in tumor burden >25% relative to nadir (minimum recorded tumor burden) which is confirmed by repeat assessment (investigator determination based on site radiology reading; SPONSOR will collect CT scans for retrospective analysis) no less than four weeks from the date of the first documented PD. Once PD is confirmed, initial date of PD documentation will be considered as the date of disease progression. Tumor burden is defined by irRC (Appendix 6.5).*
  - *Full resolution of ipilimumab related AEs (including irAEs) back to baseline and <10 mg/day prednisone or equivalent dose for irAEs for at least two weeks prior to first dose of study drug.*
    - *No history of severe irAEs from ipilimumab CTCAE Grade 4 requiring steroid treatment.*
    - *No history of CTCAE Grade 3 irAEs from ipilimumab requiring steroid treatment (>10 mg/day prednisone or equivalent dose) >12 weeks.*

- *Minimum of four weeks (wash out period) from the last dose of ipilimumab.*

- *Patients with BRAF V600E mutant melanoma must have also been previously treated with a BRAF and/or MEK inhibitor.*

- *Patient must have progressive disease after the most recent treatment regimen.*

In Part D of the study, patients must have a histological or cytological diagnosis of MEL with progressive locally advanced or metastatic disease that is not amenable to definitive local therapy with curative intent.

- *Patients must be naive to ipilimumab and may not have received more than 2 prior systemic treatment regimens for treatment of MEL. One of them can be a BRAF or MEK inhibitor.*

In Part E of the study, patients must have a histologically-confirmed or cytologically-confirmed diagnosis of non-small cell lung cancer.

- *First-line eligible patient must be treatment-naïve to systemic treatment.*

- *Second-line eligible patients will have experienced progression of locally advanced or metastatic NSCLC after one prior systemic platinum-containing doublet antineoplastic regime (Adjuvant therapy will count as a regime if administered within 1 year before the relapse).*

- *Patient has an estimated life expectancy of at least 12 weeks.*

2) In Part B, ~~and~~ C, *D and E* of the study, patients must have measurable disease as defined per irRC (Appendix 6.5):

   i. Tumor mass: Must be accurately measurable in 2 perpendicular diameters, with both its longest diameter and its longest perpendicular must be greater than or equal to 10 mm or 2 times the axial slice thickness. Clinical lesions will only be considered measurable when they are superficial, such as skin or palpable lymph node. *For patients who are being screened for enrollment in Part B, the ipilimumab-refractory cohort, clinical lesions alone will not be considered as sufficient for enrollment; there must be measurable disease evident on CT imaging.*

6) Patient (Parts A, B, ~~and~~ C, D and E) has voluntarily agreed to participate by giving written informed consent. For Parts B, ~~and~~ C, D, and E, patient has ~~voluntarily~~ agreed to a fresh biopsy of tumor (that can be biopsied based on investigator's assessment) and to providing the acquired tissue for biomarker analysis. *Tissue obtained for the biopsy must not be previously irradiated.*

2.3 Patient Exclusion Criteria

1) Sub-bullet:

- Patient who has had ipilimumab therapy may be enrolled in Part B or Part C of the study (after 13 ipilimumab naïve patients are enrolled *in Part B*) if ~~time from last treatment is >6 weeks and~~ the ~~other~~ requirements specified in Inclusion Criterion 1) are met.

6) Sub-bullet:

- Note: The time requirement for no evidence of disease for 5 years does not apply to the tumor for which a patient is enrolled in the study. The time requirement also does not apply to patients who underwent successful definitive resection of basal cell carcinoma of the skin, superficial bladder cancer, squamous cell carcinoma of the skin, ~~or~~ in situ cervical cancer, or *other in situ cancers.*

2.4.1 Summary of Study Design

This is an open-label, ~~non-randomized~~, Phase I study in patients with locally advanced or metastatic MEL, NSCLC, or carcinoma. The study has *5* parts.

Part B

Part B will only enroll patients with MEL. MK-3475 will be administered at 2 mg/kg and 10 mg/kg. The dosing interval to be used in Part B for patients who consent under protocol amendment 001-02 will be repeated Q2W. These patients will continue Q2W dosing until they discontinue study therapy. For patients consented under protocol amendments 001-03, *001-04, 001-05*, or following approval of the administrative memo dated 06-Jan-2012, dosing will be Q3W. Study treatment will continue until disease progression, unacceptable toxicity, or the investigator considers it in the best interest of a patient to discontinue study therapy.

It is expected that Part B will enroll approximately 176 patients, including 76 ipilimumab-naïve patients: approximately 61 patients at 10 mg/kg; and 15 patients at 2 mg/kg. Along with approximately 40 patients who had previously received ipilimumab (at 10 mg/kg), and 40 patients who are ipilimumab refractory at 2 mg/kg and 20 patients *who are ipilimumab refractory* at 10 mg/kg. The first 13 patients *enrolled in Part B* will be required to be ipilimumab-naive.

Radiological Tumor Assessment in Part B

In general, response criteria and patient management will follow the recently described principles and guidelines for immunotherapies of solid tumors [18]. These irRC take into account the observation that some patients with MEL can have a transient tumor flare in

the first few months after start of immunotherapy with subsequent disease response. *Although all imaging studies will be reviewed by an independent imaging vendor in a retrospective fashion, all clinical decisions will be based on the interpretation of the investigator at the site treating the patient in real time.*

If imaging at 12 weeks shows a complete response (CR) or partial response (PR), tumor imaging will be repeated at approximately Week 16 to confirm response, *per irRC recommendations*. Patients will then return to regular scheduled imaging at approximately Week 24, and every 12 weeks subsequently.

If imaging at 12 weeks shows PD, it is at the discretion of the investigator to keep a patient on study treatment or to stop study treatment until repeat imaging will be repeated approximately 4 weeks later, in order to confirm PD. Patients that are deemed clinically unstable are not required to have repeat imaging for confirmation. This decision will be based on clinical judgment of a patient's overall clinical condition, including performance status, clinical symptoms, and laboratory data. If repeat imaging shows an objective response or stable disease relative to baseline, treatment with MK-3475 will continue/resume and the next imaging studies will be conducted approximately at Week 24, and every 12 weeks subsequently. If repeat imaging at Week 16 confirms PD, patients will be discontinued from study therapy.

The same paradigm for confirmatory scans of response or progression of disease 4 weeks after the initial finding is applicable to subsequent planned scanning intervals (e.g., Week 24, Week 36, etc.).

<u>Radiological Tumor Assessment in Part C</u>

If imaging at 9 weeks shows a complete response (CR) or partial response (PR), tumor imaging will be repeated at approximately Week 13 to confirm response, *per irRC recommendations*. Alternatively, patients may wait until the beginning of Week 18 for repeat imaging. Following Week 18, tumor imaging will be conducted approximately every 9 weeks subsequently.

If imaging at 9 weeks shows PD, it is at the discretion of the investigator to keep a patient on study treatment or to stop study treatment until repeat imaging will be repeated approximately 4 weeks later, in order to confirm PD. Patients that are deemed clinically unstable are not required to have repeat imaging for confirmation. This decision will be based on clinical judgment of a patient's overall clinical condition, including performance status, clinical symptoms, and laboratory data. If repeat imaging shows an objective response or stable disease relative to baseline, treatment with MK-3475 will continue/resume and the next imaging studies will be conducted approximately at Week 18, and every 9 weeks subsequently. If repeat imaging at Week 13 confirms PD, patients will be discontinued from study therapy.

The same paradigm for confirmatory scans of response or progression of disease 4 weeks after the initial finding is applicable to subsequent planned scanning intervals (e.g., Week 18, Week 27, etc.).

Part D

Part D will only enroll patients with MEL. MK-3475 will be administered at 2 mg/kg and 10 mg/kg. The dosing interval used in Part D will be Q3W. Study treatment will continue until disease progression, unacceptable toxicity, or the investigator considers it in the best interest of a patient to discontinue study therapy.

It is expected that Part D will enroll approximately 88 ipilimumab-naïve patients: approximately 44 patients at 2 mg/kg and 44 patients at 10 mg/kg. Patients will be randomized 1:1 and assigned to a treatment group manually by the Sponsor based on a computer-generated allocation schedule.

Radiological Tumor Assessment in Part D

The response criteria and patient management will follow the described principles and guidelines as per Part B.

Part E

Part E will enroll approximately 112 patients with NSCLC. For each chemotherapy combination, 28 patients will be randomized 1:1, manually by the Sponsor based on a computer-generated allocation schedule, to 2 mg/kg (14 patients) and 10 mg/kg (14 patients) using an allocation schedule generated in-house. Once a patient is eligible for treatment, the Sponsor will inform the site of the appropriate dose to administer.

Initially each chemotherapy combination will enroll 12 patients simultaneously to evaluate DLTs. These patients will be randomly assigned to either 2 mg/kg (6 patients) or 10 mg/kg (6 patients)of MK-3475. All 12 patients will then be evaluated for DLTs until completion of Cycle 1 for each combination. Each MK-3475/chemotherapy combination may proceed independently from the other combinations. Continued enrollment beyond these first 12 patients in each combination will be according to dose continuation rules as defined in Section 3.2.5.4.7.

Radiological Tumor Assessment in Part E

With the exception of imaging timelines (described below), the response criteria and patient management will follow the described principles and guidelines as per Part B.

For patients in Part E, following radiological tumor assessment at screening, the first radiological assessment of tumor response status will be performed at Week 9 (± 1 week), unless there is clinical indication warranting earlier radiologic imaging. The same imaging technique as used at baseline has to be used throughout the study.

If imaging at 9 weeks shows stable disease (SD), treatment will be continued and the next imaging studies will be conducted approximately at Week 18.

If imaging at 9 weeks shows a complete response (CR) or partial response (PR), tumor imaging will be repeated at approximately Week 13 to confirm response, per irRC recommendations. Alternatively, patients may wait until the beginning of Week 18 for repeat imaging. Following Week 18, tumor imaging will be conducted approximately every 9 weeks subsequently.

If imaging at 9 weeks shows PD, it is at the discretion of the investigator to keep a patient on study treatment or to stop study treatment until repeat imaging will be repeated approximately 4 weeks later, in order to confirm PD. Patients that are deemed clinically unstable are not required to have repeat imaging for confirmation. This decision will be based on clinical judgment of a patient's overall clinical condition, including performance status, clinical symptoms, and laboratory data. If repeat imaging shows an objective response or stable disease relative to baseline, treatment with MK-3475 will continue/resume and the next imaging studies will be conducted approximately at Week 18, and every 9 weeks subsequently. If repeat imaging at Week 13 confirms PD, patients will be discontinued from study therapy.

The same paradigm for confirmatory scans of response or progression of disease 4 weeks after the initial finding is applicable to subsequent planned scanning intervals (e.g., Week 18, Week 27, etc.).

2.4.3 Treatment Plan

Patient distribution table:

	Amendment 001-02	Amendment 001-03/04	Amendment 001-05 (new)	Total N
Part A Dose Escalation	N=10[1]			28 Solid Tumor
Part A-1	N=6[1]			
Part A-2		N=12 (Q3W)		
Part B (MEL)	**Ipilimumab naïve** at 10 mg/kg (Q2W)[2] N=46	**Ipilimumab naïve** at 10 mg/kg (Q3W) N=15		61
	Ipilimumab treated at 10 mg/kg (Q2W)[2] N=20	**Ipilimumab treated** at 10 mg/kg (Q3W) N=20		40
		Ipilimumab naïve at 2 mg/kg (Q3W) N=15		15
			Ipilimumab refractory *at 10 mg/kg (Q3W) N=20*	*20*
			Ipilimumab refractory *at 2 mg/kg (Q3W) N=40*	*40*

Part C (NSCLC)		10 mg/kg (Q3W) N=35		35
Part D (MEL)			***Ipilimumab naïve*** *at 2 mg/kg (Q3W) N=44*	*44*
			Ipilimumab naïve *at 10 mg/kg (Q3W) N=44*	*44*
Part E (NSCLC)			*1L: 2 mg/kg (Q3W) + carboplatin/ paclitaxel N=14*	*14*
			1L: 10 mg/kg (Q3W) + carboplatin/ paclitaxel N=14	*14*
			1L: 2 mg/kg (Q3W) + cisplatin/pemetrexed N=14	*14*
			1L: 10 mg/kg (Q3W) + cisplatin/pemetrexed N=14	*14*
			2L: 2 mg/kg (Q3W) + docetaxel N=14	*14*
			2L: 10 mg/kg (Q3W) + docetaxel N=14	*14*
			2L:2 mg/kg (Q3W) + pemetrexed N=14	*14*
			2L: 10 mg/kg (Q3W) + pemetrexed N=14	*14*

2L = Second line arm
1L = First line arm
1 The dosing interval between Cycle 1 and Cycle 2 is 28 days, Cycle 2 and beyond will be repeated every 14 days
2 Patients in Part B are dosed Q2W. Following approval of Amendments 001-03, 001-04, 001-05, or following approval of the administrative memo dated 06-Jan-2012, new patients will be dosed Q3W.

Section 2.5 List of Efficacy/Pharmacokinetic/Immunogenicity Measurements

The Study Flow Chart (Section 1.7) provides specific details on collection time points. Details of collection procedures are found in the Procedures Manual for this study.

Part A and B and C *and D and E*

PK measurements (for detailed PK profiling in Part A, and for assessment of C_{trough} and terminal half-life in Part B, C, *D, and E*).

Part B and C *and D and E*

2.7 Statistical Analysis Plan Summary

Efficacy Assessment

Part A: Patients' best tumor response along with tumor type and other baseline characteristics will be listed.

Part B ipilimumab-naïve: Overall response rate (RR) and disease control rate (DCR) will be used as the primary endpoints for efficacy assessment of the ipilimumab-naïve patients. A 95% confidence interval along with a one-sided p-value for testing the null hypothesis based on the binomial distribution will be provided for both primary endpoints. The trial is considered to have reached the efficacy objective in this population if the two corresponding p-values for testing the null hypothesis are less than 5% OR either one is less than 2.5% based on the Hochberg procedure [19].

Part B ipilimumab-treated and ipilimumab-refractory, Part C, Part D and Part E: RR will be the primary endpoint for efficacy assessment. A 95% confidence interval for RR will be provided for each population. Although DCR is not the primary endpoint, similar analysis will also be provided.

In addition, Kaplan-Meier plots and descriptive statistics of progression-free-survival (PFS) and overall survival (OS) will be provided. Descriptive statistics will also be provided for analysis of response duration and tumor volumetric change. Further, the 95% confidence intervals will be provided for all the efficacy endpoints of interest between 2 mg/kg and 10 mg/kg in Part D and Part E.

Sample Size Calculations

Part B ipilimumab-naïve: With 61 ipilimumab-naïve patients treated at RP2D, the study has approximately 97% power to detect an effect size of RR=25% or DCR=50% under the null hypothesis of RR=10% and DRC=30%, or >99% power to detect an effect size of RR=30% or DCR=55%, at a type I error rate of 5% (one-sided) based on the Hochberg procedure. For the subgroup of patients on same dosing schedule (Q2W or Q3W), the corresponding powers to the two effect sizes are respectively 87% and 97% when the sample size is 40, 76% and 91% when the sample size is 30, and 44% and 62% when the sample size is 15.

Part B ipilimumab-treated: With 40 patients, the study has approximately 92%/98% power to rule out a ≤5% RR (null hypothesis) when the true RR is 20%/25% at the 5% type I error rate (one-sided). The corresponding powers are 75%/90% when sample size is 30 and 59%/78% when sample size is 20 at Q3W or Q2W.

Part B ipilimumab-refractory: With 40 patients at a dose level, the study has approximately 92%/98% power to rule out a ≤5% RR (null hypothesis) when the true RR is 20%/25% at the 5% type I error rate (one-sided). Besides, with approximately 40 ipilimumab-refractory patients at each dose level (after including those enrolled prior to Amendment 05), the study has ~85% power to detect 25% vs 5% in RR between the two doses. A p-value of 10% approximately corresponds to a 13% empirical difference in RR between the two doses.

Part C NSCLC: With 35 NSCLC patients treated at RP2D, the study has approximately 80% power to rule out a ≤9% RR (null hypothesis) when the true RR is 22% at the 10% type I error rate (one-sided).

Part D ipilimumab-naïve: With 44 patients treated at 2 mg/kg and 44 treated at 10 mg/kg, the study has 80% power to detect 30% vs 10% or 90% power to detect 25% vs 5% in RR between the two dose levels at the 10% type I error rate (one-sided). A p-value of 10% approximately corresponds to a 12% empirical difference in RR.

Part E NSCLC: With 14 patients treated at a dose level for each chemotherapy combination, the study has 90% power to rule out a ≥25% DLT rate if a cutoff of ≤ 1 patient developing a DLT is used or 92% power to rule out a ≥35% DLT rate if a cutoff of ≤ 2 patients developing a DLT is used. With 56 patients at a dose level across all chemotherapy combination arms, the study has ~80% power to detect a 20% difference in RR (e.g., 40% vs 20%) at the 10% type I error rate (one-sided). A p-value of 10% approximately corresponds to a 10% empirical difference in RR.

PD-L1 biomarker effect: Kendall's tau statistic will be used for testing the PD-L1 biomarker effect for various tumor and treatment groups. All testing will be conducted at type I error rate of 2.5% (one-sided). For a sample size of 42-48 patients *with* both post-treatment disease assessments and valid evaluation of baseline PD-L1 expression levels in fresh tumor biopsies, the study has approximately 90% power to detect a one-fold difference in concordance (i.e., odds of concordance relative to discordance = 2, *or in other words tumor is twice more likely to reduce than to increase if the patient's tumor has high expression of the PD-L1 than low expression). When the sample size is reduced to* 21-28 patients, Kendall's tau has 90% power to detect a 1.5 to 2-fold difference *in concordance.*

3.1.3 Rationale for Dose

Redacted

Redacted

3.2.2 Prohibited Medications

For patients enrolled in Part E, appropriate doses of corticosteroid for use as side effect prophylaxis that are considered standard of care for the particular cytotoxic chemotherapy accompanying MK-3475 are acceptable. It is not known what effect, if any, corticosteroid at these doses may have on the efficacy of MK-3475.

3.2.5.1.2 Consent to Tumor Biopsy

An important objective of Part*s* B *and D* is to investigate biomarkers in tumor tissue that may be able to identify which melanoma patients have a high probability to benefit from treatment with MK-3475 and which do not. Thus a fresh tumor biopsy before start of study treatment is a mandatory requirement for participation in Part B *and D*. Additional tumor biopsies while on study therapy and at disease progression are highly desirable, as changes in biomarkers compared to baseline may provide meaningful insights into characteristics associated with sensitivity or resistance to MK-3475. Patients must give written consent before tumor biopsies.

Parts C *and E* will also investigate biomarkers in tumor tissue that may be able to identify which NSCLC patients have a high probability to benefit from treatment with MK-3475 and which do not. Thus a fresh tumor biopsy before start of study treatment is a mandatory requirement for participation in Parts C *and E*. Patients must give written consent before tumor biopsies. The most likely candidate biomarker (PD-L1) is most likely to be expressed later in the patient's disease course, thus a fresh sample will be needed to correlate with objective response or clinical benefit, rather than use an archival tissue block greater than two months old from the time of signing informed consent.

3.2.5.4.5 Electrocardiogram (ECG)

In Part A, a 12-lead ECG should be performed at Screening, at the Safety Follow-up Visit, and during study at the time points described in Section 1.7 (Study Flow Chart). In

Part B, a 12-lead ECG should be performed at Screening, Cycle 1, and at the Safety Follow-up Visit. In Part C, a 12-lead ECG should be performed at Screening, Cycle 1, and at the Safety Follow-up Visit. *In Parts D and E, a 12-lead ECG should be performed at Screening, Cycle 1, Cycle 2, and at the Safety Follow-up Visit*.

3.2.5.4.6 Guidelines for Study Drug Administration

Patients in Part B will receive MK-3475 at the preliminary RP2D(s) determined in Part A. The dosing interval to be used in Part B for patients who consent under protocol amendment 001-02 will be repeated Q2W. These patients will continue Q2W dosing until they discontinue study therapy. For patients consented under protocol amendments 001-03, *001-04, 001-05*, or following approval of the administrative memo dated 06-Jan-2012, dosing will be Q3W.

Patients in Part D will receive MK-3475 at 2 mg/kg and 10 mg/kg. The dosing interval will be every 3 weeks.

Patients in Part E will receive MK-3475 at 2 mg/kg and 10 mg/kg, in combination with chemotherapy. The dosing interval will be every 3 weeks.

3.2.5.4.7 Rules for Dose Escalation *and Continuation*

Rules for Part A Dose Escalation header added

Rules for Part E Dose Continuation

DLTs observed in Cycle 1 will be used to determine completion of the specific dose combination. The dose continuance rules are as follows:

- *An initial 12 patients with each combination are enrolled simultaneously. Patients are randomly assigned 1:1 to either 2 mg/kg (6 patients) or 10 mg/kg (6 patients).*
- *Following the randomization of the initial 12 patients for a combination regimen (6 patients in each combination and dose):*
    - *If ≤1/6 patients at each dose level develops a DLT, randomization will continue for the combination regimen, such that the remaining 16 patients for that combination regimen will be randomly assigned between 2 mg/kg and 10 mg/kg in a 1:1 fashion.*
    - *If 2 or 3 of 6 patients experience a DLT at 2 mg/kg, but ≤1/6 patients experience a DLT at 10 mg/kg for that combination regimen, then 1:1 randomization of an additional 16 patients will continue for that combination regimen.*
    - *If ≥4/6 patients experience a DLT, at 2 mg/kg, then further enrollment into that combination regimen will be terminated.*

- *If ≥2/6 patients experience a DLT at 10 mg/kg, then further enrollment into the combination regimen at that dose will be terminated, however, further enrollment into the 2 mg/kg cohort for that combination regimen may continue until 14 patients have been enrolled provided that ≤1/6 initial patients experienced DLTs at the 2 mg/kg combination dose. If, however, only ≤2/14 patients at 2 mg/kg experience DLTs then a further 8 patients may be enrolled into that combination regimen at 10 mg/kg and its safety will be reconsidered provided that only 2 or 3 patients experienced DLTs amongst the initial 6 patients for the combination regimen at 10 mg/kg. If 4 to 6 patients experience DLTs amongst the initial 6 patients for combination regimen at 10 mg/kg, then this combination regimen at 10 mg/kg will not be re-opened and 2 mg/kg will be declared the recommended Phase 2 dose.*
- *If ≥2/6 patients experience a DLT at both dose levels, then further enrollment into the combination regimen will be terminated.*

- *If ≤7/28 patients develop a DLT in a given combination regimen, then it will be considered acceptable for use in subsequent studies, provided that ≥4/14 patients at the 10 mg/kg dose combination do not have a DLT.*

- *If ≥8/28 patients develop a DLT in a given combination regimen, enrollment into that combination will be terminated.*

Each combination may initially enroll, and subsequently continue or be terminated, independent of the other MK-3475/chemotherapy combinations. The highest dose to be tested is 10 mg/kg.

3.2.5.4.8 Preliminary RP2D for use in Parts B, C, *D and E*

The dose to be used in Part C will be the preliminary RP2D, 10 mg/kg. The doses to be used in Parts D, and E will be 2 mg/kg and 10 mg/kg (Part E in combination with chemotherapy).

3.2.5.4.9 Guidelines for Dose Modifications

***MK-3475 will be withheld** for* the following adverse reactions:

- A drug-related non-hematological toxicity ≥Grade 2, with the exception of the adverse reactions listed under requirement of permanent discontinuation of study therapy
  - Grade 2-3 fatigue does not require the withholding of study therapy

In addition, MK-3475 will be withheld for any of the following adverse events. Permanent discontinuation should be considered following discussion with the SPONSOR:

- Severe or life-threatening adverse reactions, including any of the following:
  - Grade 4 toxicity (non-hematologic or hematologic)
  - Diarrhea with abdominal pain, fever, ileus, or peritoneal signs; increase in stool frequency (7 or more over baseline), stool incontinence, need for intravenous hydration for more than 24 hours, gastrointestinal hemorrhage, and gastrointestinal perforation
  - Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >5 times upper limit of normal
    - For patients with liver metastasis who entered the study with Grade 2 elevation of AST/ALT, MK-3475 will be permanently discontinued if AST/ALT increase ≥ 50% relative to baseline and lasting ≥1 week)
  - Total serum bilirubin >3 times upper limit of normal
  - Steven-Johnson syndrome, toxic epidermal necrolysis, or rash complicated by full thickness dermal ulceration or necrotic, bullous or hemorrhagic manifestations
  - Severe (i.e., CTCAE Grade 3 or 4) motor or sensory neuropathy, Guillain-Barré syndrome, or myasthenia gravis
  - Severe immune-related adverse events involving any other organs (e.g., nephritis, pneumonitis, pancreatitis, non-infectious myocarditis)
  - Immune-mediated ocular disease that is unresponsive to topical immunosuppressive therapy
  - Grade 4 infusion reaction
- Grade 2 **clinical** adverse reactions which persist for >4 weeks
- Inability to reduce corticosteroid dose for immune-related adverse events to <10 mg prednisone or equivalent per day.

In case toxicity does not resolve to Grade 0-1 within 12 weeks after last administration of study drug, study therapy will be discontinued. *With Investigator and Sponsor agreement, patients with a laboratory adverse event still at Grade 2 may continue in the study only if asymptomatic and controlled.* In patients who continue on study therapy after experiencing such toxicity, *if considered drug-related by the investigator*, the dosing interval in subsequent cycles will be increased by 1 week (e.g., to 3 weeks in patients who were on an every 2 week schedule).

For patients who experience a recurrence of the same severe AEs listed above with rechallenge of MK-3475, a consultation between the Sponsor and Investigator will occur to determine whether the patient should continue in the study.

Guidelines for Part E

Patients in Part E who experience a toxicity that is attributed to the chemotherapy in the investigator's opinion, may discontinue the cytotoxic chemotherapy, but may continue with MK-3475 until unacceptable toxicity or progression.

3.2.5.4.11 Supportive Care Guidelines

In Part E, refer to SOC guidance for patients receiving chemotherapy treatment.

- ~~**Infusion reaction**: Infusion reactions may consist of fever, chills/rigor, nausea, pruritus, angioedema, hypotension, headache, bronchospasm, urticaria, rash, vomiting, myalgia, dizziness or hypertension. Severe reactions may include acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, and cardiogenic shock. Patients should be closely monitored for an infusion reaction during and immediately following drug infusion.~~

  - ~~In the event of a Grade 1 or 2 infusion reaction, reduce the infusion rate by 50% for the entire remaining duration of that infusion. Proper medical management should be instituted, as indicated per type of the reaction. This includes but is not limited to an antihistamine (e.g., diphenhydramine or equivalent), anti-pyretic (e.g., paracetamol or equivalent), and if considered indicated oral or IV glucocorticoids, epinephrine, brochodilators, and oxygen.~~
  - ~~In the event of a Grade 3 or 4 infusion reaction, immediately stop the infusion. Proper medical management should be instituted immediately, as indicated per type and severity of the reaction. This includes but is not limited to oral or IV anti-histamine, anti-pyretic, glucocorticoids, epinephrine, brochodilators, and oxygen.~~

  ~~Regarding continuation of study therapy after an infusion reaction has occurred, see the guidelines in Section 3.2.5.4.9.~~

3.2.5.4.11.1 Pneumonitis

The treatment of symptomatic patients differs from asymptomatic patients. Patients with symptomatic pneumonitis should immediately stop receiving MK-3475 and have an evaluation, which may include bronchoscopy and pulmonary function tests, to rule out other causes such as infection. If the patient is diagnosed with study drug-associated pneumonitis, the following treatment plan is recommended and should be applied.

Recommended treatment for symptomatic pneumonitis:

- *Dose interruption of MK-3475 and steroid intervention for ≤Grade 2 with option to return to treatment if improves to Grade 1 or resolves within 4 weeks.*
    - *Patients should begin a regimen of steroids and taper, if necessary. MK-3475 may be resumed once clinical improvement is observed.*
- *Immediate discontinuation if ≥Grade 3.*

After improvement to ≤Grade 1 of the pneumonitis the following rules should apply:

- *First episode of pneumonitis*
    - *Improvement occurs in ≤2 weeks – dose MK-3475 at usual schedule of Q2W or Q3W.*
    - *Improvement occurs in >2 weeks – add an additional week in between MK-3475 dosing (e.g., Q3W now becomes Q4W).*
- *Second episode of pneumonitis*
    - *Permanently discontinue MK-3475 if upon rechallenge patient develops pneumonitis ≥Grade 2.*

If there is no improvement in the signs of pneumonitis additional diagnostic procedures should be considered, such as bronchoscopy, to confirm the diagnosis.

3.2.5.4.11.2 Immune-related Adverse Events

irAE may be defined as an adverse event of unknown etiology, associated with drug exposure and is consistent with an immune phenomenon. Efforts should be made to rule out neoplastic, infectious, metabolic, toxin or other etiologic causes prior to labeling an adverse event an irAE. Immunological, serological and histological (biopsy) data should be used to support the diagnosis of an immune-related toxicity. If an irAE is noted, appropriate work-up (including biopsy if possible) should be performed.

Patients who develop a G2 or higher irAE (e.g., colitis, skin rash, hepatitis, uveitis, hypo- or hyperthyroidism, hypophysitis, renal toxicity, pneumonitis, or any other), should be discussed immediately with the SPONSOR. Depending on the type and severity of an irAE, oral or intravenous treatment with a corticosteroid should be considered, in addition to appropriate symptomatic treatment of a given condition.

Patients should be assessed for possible irAEs prior to each dose. Lab results should be evaluated and patients should be asked for signs and symptoms suggestive of an irAE. Patients who develop irAEs should have additional testing to rule out other etiologic causes. If lab results or symptoms indicated a possible irAE then additional testing should be performed to rule out other etiologic causes. If no other cause was found then it is assumed to be an irAE.

3.2.5.4.12 Duration of Therapy

In Part E, Refer to SOC guidance for patients receiving chemotherapy treatments.

3.2.5.4.13 Safety Follow-up Visit

After a patient is discontinued from study therapy (in Parts *A, B, C, D, and E*), a mandatory Safety Follow-Up Visit should be performed approximately 30 days after the last infusion of study medication. Procedures and assessments performed at the Safety Follow-Up Visit and beyond should follow the respective guidelines described in the Study Flow Chart (Section 1.7) for Parts A, *B, C, D, and E* as appropriate.

3.2.5.4.14 Duration of Follow-up

In all patients in Part A, every effort should be made to collect blood samples for PK every 4-8 weeks and antibodies to MK-3475 approximately every 2 months after last drug administration, for a total period of 24 weeks. In Parts B, *C, D, and E,* every effort should be made to collect blood samples for PK and antibodies to MK-3475 approximately every 12 weeks, for a total period of 24 weeks after last drug administration. The first collection of blood samples can be performed at the time of the mandatory Safety Follow-Up Visit.

In Parts B, *C, D, and E,* patients who discontinued study therapy without documented disease progression, monitoring of their disease status by radiologic imaging should continue following the guidelines described in the Study Flow Chart (Section 1.7; Parts B, *C, D, and E*: Follow-Up). Disease monitoring should continue (1) for approximately 6 months without disease progression, (2) until start of a new anti-cancer treatment, (3) until documented disease progression, or (4) until death, whichever occurs first.

Patients will be followed long-term for survival, as described in the Study Flow Chart (Section 1.7; *Parts C, D, and E: Follow-Up*)

3.3.1.1 Response Criteria

For Parts A, B, C, D, and E, tumor response will be determined by investigator assessment with retrospective independent central review.

In Part D, the irRC will be applied as the primary measure for assessment of tumor response and as basis for all protocol guidelines related to disease status (e.g., discontinuation of study therapy). The irRC system is specifically described in the IIOM and in Appendix 6.5. RECIST 1.1 will be applied as a secondary measure. In addition, evaluation of volumetric tumor response will be performed by a central imaging vendor (see IIOM for details).

In Part E, the irRC will also be applied as the primary measure for assessment of tumor response and as basis for all protocol guidelines related to disease status (e.g., discontinuation of study therapy). The irRC system is specifically described in the IIOM

and in Appendix 6.5. RECIST 1.1 will be applied as a secondary measure. In addition, evaluation of volumetric tumor response will be performed by a central imaging vendor (see IIOM for details).

3.3.1.2 Efficacy Endpoints

Part B

The primary endpoint for MEL patients previously treated with ipilimumab *and refractory to ipilimumab* is RR. All other endpoints as defined above will serve as secondary endpoints.

Part D

In Part D, the primary endpoint for MEL patients used to determine anti-tumor activity is RR. RR will include patients with CR or PR.

Secondary efficacy endpoints determined in Part D will include DCR, duration of response, PFS and OS. Duration of response will be measured from first documentation response to first documentation of disease progression. PFS will be measured from start of treatment to documentation of definitive disease progression as defined by irRC or death due to any cause, whichever occurs first. Survival will be measured from start of treatment to death due to any cause.

Part E

In Part E, the primary endpoint for NSCLC patients used to determine anti-tumor activity is RR. RR will include patients with CR or PR.

Secondary efficacy endpoints determined in Part E will include duration of response, PFS and OS. Duration of response will be measured from first documentation response to first documentation of disease progression. PFS will be measured from start of treatment to documentation of definitive disease progression as defined by irRC or death due to any cause, whichever occurs first. Survival will be measured from start of treatment to death due to any cause.

3.3.1.3 Radiographic Assessment

In *all* patients (*Parts A, B, C, D, and E*), baseline tumor imaging (CT or MRI, with a preference for CT) examinations must be performed within 30 days before enrollment. The same imaging technique as used at baseline has to be used throughout the study.

Part B

If disease assessment at Week 12 shows a CR or PR, imaging will be repeated at Week 16 to confirm response, *per irRC recommendations*. Subsequent imaging will be performed at Week 24.

If imaging at 12 weeks shows PD, it is at the discretion of the investigator to keep a patient on study treatment or to stop study treatment until repeat imaging will be repeated approximately 4 weeks later, in order to confirm PD. Patients that are deemed clinically unstable are not required to have repeat imaging for confirmation. This decision will be based on clinical judgment of a patient's overall clinical condition, including performance status, clinical symptoms, and laboratory data. If repeat imaging shows an objective response or stable disease relative to baseline, treatment with MK-3475 will continue/resume and the next imaging studies will be conducted approximately at Week 24, and every 12 weeks subsequently. If repeat imaging at Week 16 confirms PD, patients will be discontinued from study therapy.

The same paradigm for confirmatory scans of response or progression of disease 4 weeks after the initial finding is applicable to subsequent planned scanning intervals (e.g., Week 24, Week 36, etc.). After Week 24, imaging will be repeated every 12 weeks +/- 1 week.

Part C

If imaging at 9 weeks shows a complete response (CR) or partial response (PR), tumor imaging will be repeated at approximately Week 13 to confirm response, *per irRC recommendations*. Alternatively, patients may wait until the beginning of Week 18 for repeat imaging. Following Week 18, tumor imaging will be conducted approximately every 9 weeks subsequently.

If imaging at 9 weeks shows PD, it is at the discretion of the investigator to keep a patient on study treatment or to stop study treatment until repeat imaging will be repeated approximately 4 weeks later, in order to confirm PD. Patients that are deemed clinically unstable are not required to have repeat imaging for confirmation. This decision will be based on clinical judgment of a patient's overall clinical condition, including performance status, clinical symptoms, and laboratory data. If repeat imaging shows an objective response or stable disease relative to baseline, treatment with MK-3475 will continue/resume and the next imaging studies will be conducted approximately at Week 18, and every 9 weeks subsequently. If repeat imaging at Week 13 confirms PD, patients will be discontinued from study therapy.

The same paradigm for confirmatory scans of response or progression of disease 4 weeks after the initial finding is applicable to subsequent planned scanning intervals (e.g., Week 18, Week 27, etc.).

Part D

In Part D, the response criteria and patient management will follow the described principles and guidelines as per Part B.

Part E

In Part E, the response criteria and patient management will follow the described principles and guidelines as per Part C.

3.3.2 Pharmacokinetic Measurements

Part D

In Part D, PK profile of MK-3475 will be further characterized using a population modeling approach.

The time points for PK blood sampling are described in Section 1.7 (Part D Study Flow Charts for 2 weeks and 3 weeks).

Part E

In Part E, PK profile of MK-3475 will also be further characterized using a population modeling approach.

The time points for PK blood sampling are described in Section 1.7 (Part E Study Flow Chart).

3.4.8 Events of Clinical Interest

Immune-related Adverse Events

Patients who develop a G3 or higher irAE (e.g., colitis, skin rash, hepatitis, uveitis, hypo- or hyperthyroidism, hypophysitis, renal toxicity, pneumonitis, or any other), should be discussed immediately with the SPONSOR and reported as an event of clinical interest. Depending on the type and severity of an irAE, oral or intravenous treatment with a corticosteroid should be considered, in addition to appropriate symptomatic treatment of a given condition.

3.5.2 Hypotheses/Estimation

There is no historical data to benchmark patients previously treated with ipilimumab *or patients refractory to ipilimumab*. The null hypothesis on RR is chosen to be ≤5% *(a RR of no interest for further clinical development for this antibody as a monotherapy),* and the alternative hypothesis is chosen to be 20%/25%. *For Part C* NSCLC patients, the null hypothesis on RR is chosen to be ≤9%, and the alternative hypothesis is chosen to be 22%.

3.5.3.1 Efficacy Endpoints

The primary endpoint *is RR* for *Part B ipilimumab-treated, Part C, Part D, and Part E*. All other endpoints as defined above will serve as secondary endpoints.

3.5.3.4 Predictive Biomarker Endpoints

The primary candidate biomarker to be investigated in *this* study is PD-L1 expression levels in tumor tissue at baseline, which will be assessed by IHC.

3.5.4.1 Efficacy Analysis

The primary efficacy analyses will be based on the Full Analysis Set (FAS) population for each of the sub-populations (ipilimumab-naïve patients in Part B, *ipilimumab-refractory patients in Part B,* patients previously treated with ipilimumab in Part B and NSCLC patients in Part C, *ipilimumab-naïve patients in Part D, and NSCLC patients in Part E*). Patients with measurable disease at baseline who received at least one dose of study treatment will be included in the FAS population. *The primary analyses of ipilimumab-refractory patients are based on patients who meet the definition of ipilimumab-refractoriness, irrespective of which amendment they are enrolled to. A subgroup analysis will be conducted for all patients randomized in Amendment 05.*

3.5.4.2 Safety Analysis

The All Patients as Treated (APaT) population will be used for the analysis of safety data in this study. The APaT population consists of all patients who received at least 1 dose of study treatment in Part A, Part B, Part C, *Part D, and Part E.*

In order for a patient to be considered evaluable for the analysis of DLT, the patient must have either had a DLT in Cycle 1 or had received at least 90% of the prescribed dose of MK-3475 in Cycle 1 and completed all safety evaluations up to and including at least 28 days after the first administration of MK-3475 without experiencing a DLT. *A patient without a DLT will replaced if he/she did not adequately complete the evaluation period associated with the first cycle of study therapy (i.e., discontinue prematurely due to a reason unrelated to study therapy) or if that patient received <90% of the prescribed dose.*

3.5.4.4 Predictive Biomarker Analysis

The primary predictive biomarker analysis is based on a subset of the FAS population in Part B, Part C, *Part D, and Part E* that includes patients with both a valid PD-L1 expression measurement and at least one disease assessment post-treatment.

3.5.5.1 Efficacy Analysis

Part B ipilimumab-naïve: Overall response rate (RR) and disease control rate (DCR) will be used as primary endpoints for efficacy assessment of the ipilimumab-naïve patients. A 95% confidence interval along with a one-sided p-value for testing the null hypothesis based on the binomial distribution will be provided for each for the two primary endpoints: overall RR and overall DCR. Similar analyses will be provided for interim analyses of RR and DCR at week 12. Exploratory analyses will be conducted to compare the PFS rate at 6-month and OS rate at 1-year with historical control as well as with the recent ipilimumab data adjusted with baseline factors such as ECOG [75].

Part B ipilimumab-treated, Part B ipilimumab-refractory, Part C, Part D, and Part E: RR will be the primary endpoint for efficacy assessment. A 95% confidence interval for RR will be provided for each population and by dose level as applicable. Although DCR is not the primary endpoint, similar analyses will also be provided.

In addition, Kaplan-Meier plots and descriptive statistics of progression-free-survival (PFS) and overall survival (OS) will be provided. Descriptive statistics will also be provided for analysis of response duration and tumor volumetric change. Further, the 95% confidence intervals will be provided for all the efficacy endpoints of interest between 2 mg/kg and 10 mg/kg in Part B ipilimumab-refractory patients and Part D ipilimumab-naïve patients. Although efficacy assessment is not the primary objective of Part E, the 95% confidence intervals for all the efficacy endpoints of interest between 2 mg/kg and 10 mg/kg will also be provided.

3.5.5.4 Predictive Biomarker Analysis

As an exploratory predictive biomarker analysis, patients will be categorized into "biomarker positive" and "biomarker negative" populations based on their PD-L1 expression levels being above or below a cut-off point. A ROC curve of true positive rate versus false positive rate and other graphic tools will be provided to help determine a cut-off point of PD-L1 expression level that best distinguishes between "biomarker positive" and "biomarker negative" populations with respect to RR and DCR. A multivariate logistic regression analysis will be conducted to assess the cut-off point after adjustment of important baseline characteristics. Covariates in the regression model will include PD-L1 expression category ("biomarker positive" or "biomarker negative"), gender, age category (above or below median), ECOG performance status (0 or 1), LDH (≤ upper limit of the normal range OR > upper limit of the normal range or unknown), number of previous systemic therapies (< or ≥ median) and other prognostic factors and predictive biomarkers as appropriate. An estimate of treatment difference between the "biomarker positive" population and the "biomarker negative" population from the model, along with a nominal 95% confidence interval will be provided. Notice that the estimate of treatment difference may be biased due to intrinsic differences between the two populations that cannot be adequately accounted for in a model, and the 95% confidence interval may not have a 95% coverage rate unless the cut-off point is solely derived from external data. *To increase the rigor of hypothesis testing, a tentative cut-off point is set at 5% expression level based on a recent publication [76]*.

3.5.5.5 Safety Analysis

The 80% *confidence intervals and Bayes credible intervals* for DLT and drug-related toxicity rates in Cycle 1 for an identified MTD level will be provided. Summary statistics (median and range) for time to onset of first drug-related toxicity in each dose level will be provided. Adverse experiences will be summarized as counts and frequencies for each dose level. Laboratory assessments, vital signs, and other safety endpoints will be summarized as appropriate.

3.5.6 Multiplicity

The predictive biomarker hypothesis on PD-L1 will be formally tested at a type I error rate of 2.5% (one-sided) separately *for each part of the study*, irrespective of the outcome from efficacy analyses. Once the null hypothesis is rejected, a step-down procedure may be applied to the testing of other biomarker hypotheses prospectively specified before the end of the study (in a separate document). While additional exploratory analyses will be conducted to evaluate alternative predictive biomarkers, there is no multiplicity control of such analyses and no formal conclusion can be made.

The efficacy hypothesis is tested at 5% (one-sided) for *Part B* ipilimumab-naïve population and ipilimumab-treated population, at 10% (one-sided) for *Part C* NSCLC population *and at 10% for between-dose comparison in Part D ipilimumab-naive population, Part B ipilimumab-refractory population and Part E NSCLC population. .*

Sample Size and Power Calculations

Part B ipilimumab-naïve: With 61 ipilimumab-naïve patients treated at RP2D, the study has approximately 97% power to detect an effect size of RR=25% or DCR=50% under the null hypothesis of RR=10% and DRC=30%, or >99% power to detect an effect size of RR=30% or DCR=55%, at a type I error rate of 5% (one-sided) based on the Hochberg procedure. For the subgroup of patients on same dosing schedule (Q2W or Q3W), the corresponding powers to the two effect sizes are respectively 87% and 97% when the sample size is 40, 76% and 91% when the sample size is 30, and 44% and 62% when the sample size is 15.

Part B ipilimumab-treated: With 40 patients, the study has approximately 92%/98% power to rule out a ≤5% RR (null hypothesis) when the true RR is 20%/25% at the 5% type I error rate (one-sided). The corresponding powers are 75%/90% when sample size is 30 and 59%/78% when sample size is 20 at Q3W or Q2W.

Part B ipilimumab-refractory: With 40 patients at a dose level, the study has approximately 92%/98% power to rule out a ≤5% RR (null hypothesis) when the true RR is 20%/25% at the 5% type I error rate (one-sided). Besides, with approximately 40 ipilimumab-refractory patients at each dose level (after including those enrolled prior to Amendment 05), the study has ~85% power to detect 25% vs 5% in RR between the two doses. A p-value of 10% approximately corresponds to a 13% empirical difference in RR.

Part C NSCLC: With 35 NSCLC patients treated at RP2D, the study has approximately 80% power to rule out a ≤9% RR (null hypothesis) when the true RR is 22% at the 10% type I error rate (one-sided).

Part D ipilimumab-naïve: With 44 patients treated at 2 mg/kg and 44 treated at 10 mg/kg, the study has 80% power to detect 30% vs 10% or 90% power to detect 25% vs 5% in RR between the two dose levels at the 10% type I error rate (one-sided). A p-value of 10% approximately corresponds to a 12% empirical difference in RR.

Part E NSCLC: With 14 patients treated at a dose level for each chemotherapy combination, the study has 90% power to rule out a ≥25% DLT rate if a cutoff of ≤ 1 patient developing a DLT is used or 92% power to rule out a ≥35% DLT rate if a cutoff of ≤ 2 patients developing a DLT is used. With 56 patients at a dose level across all chemotherapy combination arms, the study has ~80% power to detect a 20% difference in RR (e.g., 40% vs 20%) at the 10% type I error rate (one-sided). A p-value of 10% approximately corresponds to a 10% empirical difference in RR.

PD-L1 biomarker effect: Kendall's tau statistic will be used for testing the PD-L1 biomarker effect for various tumor and treatment groups. All testing will be conducted at type I error rate of 2.5% (one-sided). For a sample size of 42-48 patients with both post-treatment disease assessments and valid evaluation of baseline PD-L1 expression levels in fresh tumor biopsies, the study has approximately 90% power to detect a one-fold difference in concordance (i.e., odds of concordance relative to discordance = 2, or in other words tumor is twice more likely to reduce than to increase if the patient's tumor has high expression of the PD-L1 than low expression). When the sample size is reduced to 21-28 patients, Kendall's tau has 90% power to detect a 1.5 to 2-fold difference in concordance.

3.5.7 Subgroup Analysis and Effect of Baseline Factors

In assessment of anti-tumor activity in *melanoma* population, patients will be analyzed by treatment history with ipilimumab and by dose level and dosing interval (Q2W or Q3W). *In addition, ipilimumab-naïve patients treated at 2 mg/kg Q3W and 10 mg/kg Q3W in Part B will be combined with those in Part D for a sensitivity analysis of treatment difference between the two doses. In assessment of anti-tumor activity in the NSCLC population, patients will be analyzed by line of therapy and by dose level.*

In assessment of the predictive biomarkers, *subgroup analyses* by gender, age category (above or below median) and ECOG performance status (0 or 1) will be *conducted to mitigate confounding effect*. Exploratory analyses will also be conducted to compare DCR and RR between "biomarker positive" and "biomarker negative" populations determined by the cut-off point of PD-L1 expression level.

3.6.1 Patients and Replacements Information

MK-3475 clinical supplies will be packaged to support enrollment of approximately *439* patients.

All other medications will be provided by the Investigator.

3.6.2 Primary Packaging and Labeling Information

Investigational materials will be provided by the SPONSOR as summarized in *Table 3-6*.

MK-3475 (SCH900475) supplies will be packaged in **glass vials** as described in Table 3-7 below.

Product: MK-3475 1
Protocol/Amendment No.: 001-06

SUMMARY OF CHANGES

PRIMARY REASON(S) FOR THIS AMENDMENT

The primary objectives of this amendment are the increase in sample size of Part B, the modification of Part E, and addition of Part F. These changes are primarily encompassed by the following:

Part E: Characterize the safety profile and tolerability and evaluate the clinical activity of MK-3475 in patients whose tumors express PD-L1 with non-small cell lung cancer (NSCLC) in combination with chemotherapy in a first line setting at the preliminary doses of 2 mg/kg, 5 mg/kg, and 10 mg/kg.

Part F: Characterize the safety profile and tolerability of MK-3475 and evaluate the clinical activity of MK-3475 in patients whose tumors express PD-L1 with non-squamous NSCLC at the preliminary doses of 2 mg/kg and 10 mg/kg.

Implementation of these objectives necessitates the following changes to the protocol:

- Addition of 100 ipilimumab-refractory patients with melanoma in Part B.
- Increase to 146 patients with non-small cell lung cancer in Part E, utilizing only first line chemotherapy combinations.
- Addition of 120 patients with non-squamous NSCLC in Part F including the addition of all Part F-specific procedures.

ADDITIONAL CHANGE(S) FOR THIS AMENDMENT

Throughout the protocol, procedures have been separately listed for Part A, Part B, Part C, Part D, Part E and Part F. Changes specific to the conduct of Part A, B, C, D, E and F are listed here. Part F text should be reviewed in its entirety throughout the protocol.

In addition, typographical errors and inconsistencies were corrected throughout the document and are not listed here. Protocol sections that include changes relevant to Part A, Part B, Part C, Part D, Part E and Part F but do not impact study conduct of these Parts are not listed here (e.g., 1.3 Summary of Rationale, 3.1.2 Rationale for This Study, 3.1.3 Rationale for Dose) and should be reviewed in their entirety.

Throughout the document, MDX-1106 (BMS-936558) has been updated to nivolumab. This change is not listed here.

Product: MK-3475 2
Protocol/Amendment No.: 001-06

Section 1.2 Indication

For Part E, patients *whose tumors express PD-L1* with a histologically or cytologically confirmed diagnosis of non-small cell lung cancer (NSCLC) with progressive locally advanced or metastatic disease ~~after 1 prior systemic platinum-containing doublet therapy regimen or~~ naïve to systemic treatment. *These patients will receive MK-3475 in combination with cytotoxic chemotherapy.*

For Part F, patients whose tumors express PD-L1 with a histologically or cytologically confirmed diagnosis of non-squamous non-small cell lung cancer (NSCLC) with progressive locally advanced or metastatic disease after two or more prior systemic treatment regimens or naïve to systemic treatment.

Section 1.3 Summary of Rationale

Redacted

Redacted

Section 1.4 Summary of Study Design

This is an open-label, Phase I study of intravenous (IV) MK-3475 in patients with progressive locally advanced or metastatic carcinomas, especially MEL or NSCLC. **Part A** of the study will use a traditional 3+3 design for dose escalation. Cohorts of 3-6 patients will be enrolled sequentially at escalating doses of 1, 3 and 10 mg/kg. Dose escalation will continue until identification of MTD, up to a maximum dose of 10 mg/kg. Once the dose escalation is completed, additional patients will be enrolled to more fully characterize the PK profile. In **Part B**, patients with MEL will be enrolled at the preliminary RP2D(s) to characterize the tolerability and safety profile of the dose, and for preliminary evaluation of anti-tumor activity in MEL. In **Part C**, patients with NSCLC will be enrolled at the preliminary RP2D(s) to characterize the tolerability and safety profile of the dose, and for preliminary evaluation of anti-tumor activity in NSCLC. In **Part D**, patients with MEL will be enrolled at 2 mg/kg and 10 mg/kg to evaluate the tolerability and safety profile of each dose, and for preliminary evaluation of anti-tumor activity in MEL. In **Part E**, patients *whose tumors express PD-L1* with NSCLC will be enrolled at 2 mg/kg, *5 mg/kg* and 10 mg/kg to characterize the tolerability and safety profile of MK-3475 in combination with chemotherapy, and for preliminary evaluation of the dose and anti-tumor activity in NSCLC. *Part E will also evaluate the extent of tumor response that correlates with the degree of biomarker positivity in patients treated with MK-3475 in combination with chemotherapies. In **Part F**, patients whose tumors express PD-L1 with non-squamous NSCLC will be enrolled at 2 mg/kg and 10 mg/kg to characterize the tolerability and safety profile of MK-3475 monotherapy, and for preliminary evaluation of the dose and anti-tumor activity in NSCLC. Part F will also evaluate the extent of tumor response that correlates with the degree of biomarker positivity in patients treated with MK-3475.*

Section 1.5 Sample

A total of approximately *693* eligible patients will be enrolled in this study, with approximately 28 patients in Part A, approximately *276* patients in Part B, approximately 35 patients in Part C, approximately 88 patients in Part D, approximately *146* patients in Part *E and approximately 120 patients in Part F*.

In Part B, only patients with MEL may be enrolled (metastatic MEL or patients with locally advanced disease and not candidates for surgical resection or a definitive local therapy), and patients must have measurable disease (see Section 2.2 and Appendix 6.5). Part B will enroll approximately *276* patients distributed as described in Table 1-1:

Table 1-1

Patient Distribution in Part B

	10 mg/kg	2 mg/kg
Ipilimumab Naïve	61[1]	15[2]
Ipilimumab Treated	40[1]	0
Ipilimumab Refractory	*80*[2]	*80*[2]
1 Includes patients with dosing schedules of Q2W and Q3W. 2 Dosing schedule is Q3W		

Enrollment of the first 13 patients in Part B will be restricted to ipilimumab-naïve patients (which will serve as basis for the first interim analysis). The remaining patients will be enrolled without a hold to complete a total of 60 patients (40 ipilimumab-naïve and 20 ipilimumab-treated). With amendment 04, an additional 55 patients (35 ipilimumab-naïve and 20 ipilimumab-treated) will be enrolled. *With amendment 05, 60 ipilimumab-refractory patients will be enrolled. The ipilimumab-naïve, ipilimumab-treated and ipi-refractory cohorts are defined per eligibility criteria in Sections 2.2 and 2.3. Upon approval of amendment 06, the ipilimumab-refractory cohort will enroll an additional 100 patients for a total of 160* patients. *The ipilimumab-refractory cohort* will randomize up to *80* patients at 2 mg/kg and *80* patients at 10 mg/kg who meet the ipilimumab-refractory eligibility criteria as provided in the current amendment in a *1*:1 fashion, manually by the Sponsor, based on a computer-generated allocation schedule. If a patient is ipilimumab-refractory and BRAF V600 mutant, then one of the prior systemic treatment regimens must have *included* a BRAF and/or MEK inhibitor. Ipilimumab naïve patients are allowed up to 2 prior systemic treatment regimens, one of which may have *included* prior treatment with a BRAF inhibitor.

Enrollment in Part D will be restricted to ipilimumab-naïve patients who are allowed up to 2 prior systemic treatment regimens, one of which may have *included* prior treatment with a BRAF inhibitor.

In Part E, *146* patients with NSCLC may be enrolled, and patients must have measurable disease (see Section 2.2 and Appendix 6.5). Eligible patients include metastatic or locally advanced NSCLC who are treatment naïve *systemically.*

There will be two different chemotherapy doublets that may be paired with up to three doses of MK-3475; carboplatin/paclitaxel with 2, 5 and 10 mg/kg and cisplatin/pemetrexed with 10 mg/kg, allowing for 4 cohorts. Patients receiving carboplatin/paclitaxel will be randomized *1:1:1*, manually by the Sponsor based on a computer-generated allocation schedule, to *receive additionally* either 2, 5, or 10 mg/kg of MK-3475. *The cisplatin/pemetrexed and carboplatin/paclitaxel patients will be enrolled in parallel (with choice of chemotherapy left to the investigator's discretion). However once a cohort reaches its maximum patient allotment, enrollment into that*

cohort will be closed. Each MK-3475 *carboplatin/paclitaxel* combination cohort will be limited to *44 patients (132 total patients), while 14 patients will be enrolled with MK-3475 in combination with cisplatin/pemetrexed.* Enrollment will be competitive into each cohort. *All patients in Part E must have tumors that express PD-L1 as determined by IHC using a laboratory developed assay performed during Screening. Specifics regarding the test and cut-point can be found in the Procedures Manual. All patients will be dosed Q3W.*

In Part F, 120 patients with non-squamous metastatic or locally advanced NSCLC may be enrolled, and patients must have measureable disease (see Section 2.2 and Appendix 6.5). Eighty-eight patients will be treatment naïve systemically, and 32 patients will have received at least two prior systemic therapies. Patients who are treatment naïve systemically will be randomized 1:1, manually by the Sponsor based on a computer generated allocation schedule, to either 2 or 10 mg/kg. Patients who have had at least two prior systemic therapies for their lung cancer will be treated at 10 mg/kg of MK-3475. Enrollment into the treatment naïve and previously treated cohorts will occur concurrently. All patients in Part F must have tumors that express PD-L1 as determined by IHC using a laboratory developed assay performed during Screening. Specifics regarding the test and cut-point can be found in the Procedures Manual. All patients will be dosed Q3W.

Section 1.6 Dosage/Dosage Form, Route, and Dose Regimen

MK-3475 will be administered as a 30 minute IV infusion, with a window of -5 and +10 minutes (except as indicated in Part A-2). *Study therapy for patients in all study parts will continue until disease progression or unacceptable toxicity. However in the event of a confirmed complete response (CR), it is at the discretion of the investigator to keep a patient on study treatment or to discontinue study treatment based on the following guidelines. This decision will be based on the clinical judgment of a patient's overall clinical condition, including performance status, clinical symptoms, and laboratory data. Patients who have a confirmed complete response by two scans ≥4 weeks apart and who have been on MK-3475 treatment for at least 6 months may discontinue MK-3475 treatment at the discretion of the investigator after receiving at least two doses beyond the initial determination of CR. MK-3475 may be resumed upon disease recurrence in these patients except in the case of chemotherapy combination (patients in Part E), chemotherapy will not resume. See Section 3.2.5.1.13 for details regarding follow up for CR patients who discontinue treatment with MK-3475.*

In Part B, MK-3475 will be administered at the preliminary RP2D(s) as per Section 1.5. For patients who consent under protocol amendment 001-02, dosing will be repeated Q2W *at 10 mg/kg.* For patients consented under protocol amendments 001-03, 001-04, 001-05, *001-06,* or following approval of the administrative memo dated 06-Jan-2012, dosing in Part B will be repeated Q3W *at 2 mg/kg and 10 mg/kg*. ~~Study therapy will continue until disease progression or unacceptable toxicity.~~ Patients who initiate therapy on the 2 week schedule will not switch to the 3 week schedule.

In Part E, MK-3475 will be administered at either 2, *5, or* 10 mg/kg in combination with chemotherapy. Dosing of MK-3475, and the corresponding chemotherapy will be repeated Q3W. *MK-3475 and cytotoxic chemotherapy administration will be staggered in Cycle 1 only. The initial dose of MK-3475 will be administered at Week -1 (Cycle 1) without the accompanying cytotoxic chemotherapy. At Week 0 (Cycle 1), either carboplatin/paclitaxel or cisplatin/pemetrexed will be administered while MK-3475 will be withheld.* A maximum of *three additional* cycles *(Cycles 2, 3 and 4)* of first-line carboplatin/paclitaxel or cisplatin/pemetrexed will be administered along with MK-3475, followed by single agent MK-3475 for subsequent cycles. After completion of the platinum-containing doublet, maintenance therapy with single agent pemetrexed is permitted if the investigator thinks it is appropriate per standard of care (SOC). *Bevacizumab also may be administered concurrently with carboplatin/paclitaxel, and as part of maintenance therapy thereafter, if an investigator believes it to be in the best interests of the patient.* Determination of dose of MK-3475 in combination carboplatin/paclitaxel will be by random allocation in a *1:1:1* fashion between 2 mg/kg, *5 mg/kg or* 10 mg/kg MK-3475. *Carboplatin should be administered to target an area under the curve (AUC) of 6 mg/mL/min. Paclitaxel should be administered at a dose of 200 mg/m^2. Cisplatin should be administered at a dose of 75 mg/m^2. Pemetrexed should be administered at a dose of 500 mg/m^2. Patients receiving pemetrexed should also receive appropriate vitamin supplementation of vitamin B_{12} and folic acid.*

Listed below are the MK-3475 + chemotherapy treatment combinations:

- NSCLC: Treatment naïve (first-line treatment – 146 total patients):
    - 2 mg/kg MK-3475 + carboplatin/paclitaxel (*44* patients)
    - *5 mg/kg MK-3475 + carboplatin/paclitaxel (44 patients)*
    - 10 mg/kg MK-3475 + carboplatin/paclitaxel (*44* patients)
    - 10 mg/kg MK-3475 + cisplatin/pemetrexed (*14* patients)

Part F will be split between treatment naïve patients (F-1) and patients with 2 or more prior systemic regimens (F-2). Once the appropriate line of therapy is identified, 88 patients will be randomized 1:1 in F-1, manually by the Sponsor based on a computer generated allocation schedule, to either 2 or 10 mg/kg. F-2 will treat 32 patients at 10 mg/kg.

Section 1.7 Flow Chart

Part A, A-1 Flow Chart

This flow chart is unchanged with the following exceptions:

- Addition of procedure to Screening - Informed Consent for Future Biomedical Research Consent (optional).

- Addition of procedure to Cycle 1 – collection of Blood for Future Biomedical Research (optional).

- Footnote 19: Blood collected at predose of Cycle 1 and every month at predose until 6 months of study therapy. Analysis will be performed by a central laboratory. ~~The last RNA signature profiling sample collected will test for human leukocyte antigen (HLA).~~

- Footnote 24*: If the subject signs the Future Biomedical Research (FBR) consent, any leftover tissue that would ordinarily be discarded at the end of the main study will be retained for FBR, again providing the patient has signed the FBR consent.*

- Footnote 25: *If the subject signs the Future Biomedical Research (FBR) consent, any leftover tissue that would ordinarily be discarded at the end of the main study will be retained for FBR, again providing the patient has signed the FBR consent.*

- *Footnote 27: Informed consent for future biomedical research samples must be obtained before the DNA sample. DNA sample for analysis should be obtained predose, on Day 1 (or with the next scheduled blood draw), as the last sample drawn, on randomized subjects only, or at a later date as soon as the informed consent is obtained. This sample should only be taken once from each subject.*

Part A-2 Flow Chart

This flow chart is unchanged with the following exceptions:

- Addition of procedure to Screening - Informed Consent for Future Biomedical Research Consent (optional).

- Addition of procedure to Cycle 1 – collection of Blood for Future Biomedical Research (optional).

- Footnote 18: Blood collected at predose of Cycle 1 and every month at predose until 6 months of study therapy. Analysis will be performed by a central laboratory. ~~The last RNA signature profiling sample collected will test for human leukocyte antigen (HLA).~~

- Footnote 24: If the subject signs the Future Biomedical Research (FBR) consent, any leftover tissue that would ordinarily be discarded at the end of the main study will be retained for FBR, again providing the patient has signed the FBR consent.

- Footnote 25: *If the subject signs the Future Biomedical Research (FBR) consent, any leftover tissue that would ordinarily be discarded at the end of the main study will be retained for FBR, again providing the patient has signed the FBR consent.*

- *Footnote 27: Informed consent for future biomedical research samples must be obtained before the DNA sample. DNA sample for analysis should be obtained predose, on Day 1 (or with the next scheduled blood draw), as the last sample drawn, on randomized subjects only, or at a later date as soon as the informed consent is obtained. This sample should only be taken once from each subject.*

Part B: 2 Week Schedule Flow Chart

This flow chart is unchanged with the following exceptions:

- Addition of procedure to Screening - Informed Consent for Future Biomedical Research Consent (optional).

- Addition of procedure to Cycle 1 – collection of Blood for Future Biomedical Research (optional).

- Footnote 18: Blood collected at predose of Cycle 1 and before infusion of MK-3475 in Cycles 2, 3, 5 and 7. Analysis will be performed by a central laboratory. ~~The last RNA signature profiling sample collected will test for human leukocyte antigen (HLA).~~

- Footnote 20*: If the subject signs the Future Biomedical Research (FBR) consent, any leftover tissue that would ordinarily be discarded at the end of the main study will be retained for FBR, again providing the patient has signed the FBR consent.*

- Footnote 21: *If the subject signs the Future Biomedical Research (FBR) consent, any leftover tissue that would ordinarily be discarded at the end of the main study will be retained for FBR, again providing the patient has signed the FBR consent.*

- *Footnote 23: Informed consent for future biomedical research samples must be obtained before the DNA sample. DNA sample for analysis should be obtained predose, on Day 1 (or with the next scheduled blood draw), as the last sample drawn, on randomized subjects only, or at a later date as soon as the informed consent is obtained. This sample should only be taken once from each subject.*

Part B: 3 Week Schedule Flow Chart

This flow chart is unchanged with the following exceptions:

- Addition of procedure to Screening - Informed Consent for Future Biomedical Research Consent (optional).

- Addition of procedure to Cycle 1 – collection of Blood for Future Biomedical Research (optional).

- Addition of procedure to Cycle 1, Day 1 – collection of Human Leukocyte Antigen (HLA) sample.

- Footnote 18: Blood collected at predose of Cycle 1 and before infusion of MK-3475 in Cycles 2, 3, 5 and 7. Analysis will be performed by a central laboratory. ~~The last RNA signature profiling sample collected will test for human leukocyte antigen (HLA).~~

- Footnote 20*: If the subject signs the Future Biomedical Research (FBR) consent, an aliquot of the tissue biopsies will be designated for FBR. In addition, any leftover tissue biopsies that would ordinarily be discarded at the end of the main study will be retained for FBR, again providing the patient has signed the FBR consent.*

- Footnote 21: *If the subject signs the Future Biomedical Research (FBR) consent, any leftover tissue that would ordinarily be discarded at the end of the main study will be retained for FBR, again providing the patient has signed the FBR consent.*

- *Footnote 23: Informed consent for future biomedical research samples must be obtained before the DNA sample. DNA sample for analysis should be obtained predose, on Day 1 (or with the next scheduled blood draw), as the last sample drawn, on randomized subjects only, or at a later date as soon as the informed consent is obtained. This sample should only be taken once from each subject.*

- *Footnote 24: New patients for amendment 001-06.*

Part C: 3 Week Schedule Flow Chart

This flow chart is unchanged with the following exceptions:

- Addition of procedure to Screening - Informed Consent for Future Biomedical Research Consent (optional).

- Addition of procedure to Cycle 1 – collection of Blood for Future Biomedical Research (optional).

- Footnote 18: Blood collected at predose of Cycle 1 and before infusion of MK-3475 in Cycles 2, 3, 5 and 7. Analysis will be performed by a central laboratory. ~~The last RNA signature profiling sample collected will test for human leukocyte antigen (HLA).~~

- Footnote 20*: If the subject signs the Future Biomedical Research (FBR) consent, any leftover tissue that would ordinarily be discarded at the end of the main study will be retained for FBR, again providing the patient has signed the FBR consent.*

- Footnote 21: *If the subject signs the Future Biomedical Research (FBR) consent, any leftover tissue that would ordinarily be discarded at the end of the main study will be retained for FBR, again providing the patient has signed the FBR consent.*

- *Footnote 22: Informed consent for future biomedical research samples must be obtained before the DNA sample. DNA sample for analysis should be obtained predose, on Day 1 (or with the next scheduled blood draw), as the last sample drawn, on randomized subjects only, or at a later date as soon as the informed consent is obtained. This sample should only be taken once from each subject.*

Part D: 3 Week Schedule Flow Chart

This flow chart is unchanged with the following exceptions:

- Addition of procedure to Screening - Informed Consent for Future Biomedical Research Consent (optional).
- Addition of procedure to Cycle 1 – Blood for Future Biomedical Research (optional).
- Footnote 18: Blood collected at predose of Cycle 1 and before infusion of MK-3475 in Cycles 2, 3, 5 and 7. Analysis will be performed by a central laboratory. ~~The last RNA signature profiling sample collected will test for human leukocyte antigen (HLA).~~
- Footnote 20*: If the subject signs the Future Biomedical Research (FBR) consent, any leftover tissue that would ordinarily be discarded at the end of the main study will be retained for FBR, again providing the patient has signed the FBR consent.*
- Footnote 21: *If the subject signs the Future Biomedical Research (FBR) consent, any leftover tissue that would ordinarily be discarded at the end of the main study will be retained for FBR, again providing the patient has signed the FBR consent.*
- *Footnote 24: Informed consent for future biomedical research samples must be obtained before the DNA sample. DNA sample for analysis should be obtained predose, on Day 1 (or with the next scheduled blood draw), as the last sample drawn, on randomized subjects only, or at a later date as soon as the informed consent is obtained. This sample should only be taken once from each subject.*

Part E Flow Chart

This flow chart is unchanged with the following exceptions:

- Addition of procedure to Screening - Informed Consent for Future Biomedical Research Consent (optional).
- Screening period has been adjusted to -35 to -7 days.
- Change of urinalysis to screening, and then every 12 weeks.
- 12-Lead ECG: removed procedure from Cycle 2.

- Tumor imaging has been changed to every 6 weeks.
- Cycle 1 column expanded to include a Week -1 column. Procedures for Cycle 1 have been adjusted to be completed in Week -1, Week 0, or both.
- Addition of procedures - Administer Chemotherapy, procedure added at all cycles
- Addition of procedure to Cycle 1 – Blood for Future Biomedical Research (optional)
- Addition of procedure to Cycle 1 – collection of Human Leukocyte Antigen (HLA) sample
- Footnote 5: Electrocardiogram (12-lead ECG) should be performed at Screening, prior to dosing in Cycle 1, at the time of PK blood collection for PK (Cmax) within 30 minutes after the end of the first infusion of MK-3475. *Triplicate 12-lead ECG measurements should be collected at the pre-dose and post dose at Cycle 1. Only 1 measurement is required at Screening.*
- Footnote 7: See Appendix 6.1 for list of laboratory tests. Routine laboratory tests (e.g., CBC with differential; comprehensive serum chemistry panel; urinalysis) will be performed by the local study site laboratory or their contract laboratory. Following Week 36, urinalysis should be performed every *12* weeks. CBC, serum chemistry and urinalysis may be collected up to 48 hours prior to any Cycle "X", Day 1 dosing.
- Footnote 18: Blood collected at predose of Cycle 1 and before infusion of MK-3475 in Cycles 2, 3, 5 and 7. Analysis will be performed by a central laboratory. ~~The last RNA signature profiling sample collected will test for human leukocyte antigen (HLA)~~
- Footnote 19: Tumor imaging (either CT or MRI, with strong preference for CT) will be performed within 30 days prior to enrollment. The same imaging technique has to be used in a patient throughout the study. After first documentation of progression, repeat imaging is required approximately 4 weeks later for confirmation, as per immune related response criteria (irRC) guidelines (see Appendix 6.5). *If Week 6 imaging indicates a response (CR or PR)* (see Section 2.4.1), *patients may wait until Week 12* for repeat imaging. Response status will be assessed by the study site and by a central imaging vendor. The process for collection of CT images and transmission to the central vendor for purpose of central response review is described in the Procedures Manual. Following Week 36, tumor imaging will be performed approximately every *6* weeks (or whenever clinically indicated) while the patient remains on study therapy.

- Footnote 20: *If the subject signs the Future Biomedical Research (FBR) consent, any leftover tissue that would ordinarily be discarded at the end of the main study will be retained for FBR, again providing the patient has signed the FBR consent.*

- Footnote 21: *If the subject signs the Future Biomedical Research (FBR) consent, any leftover tissue that would ordinarily be discarded at the end of the main study will be retained for FBR, again providing the patient has signed the FBR consent.*

- *Footnote 23: Patients receiving carboplatin/paclitaxel may receive bevacizumab for the first 4 cycles and beyond every 3 weeks. Patients receiving either carboplatin/paclitaxel or cisplatin/pemetrexed may receive pemetrexed Q3W as maintenance therapy once the first four cycles of the platinum-containing doublet have completed.*

- *Footnote 24: Informed consent for future biomedical research samples must be obtained before the DNA sample. DNA sample for analysis should be obtained predose, on Day 1 (or with the next scheduled blood draw), as the last sample drawn, on randomized subjects only, or at a later date as soon as the informed consent is obtained. This sample should only be taken once from each subject.*

<u>Details of Sampling for Pharmacokinetics for Patients Receiving 10 mg/kg MK-3475 + Docetaxel in Part E</u>

This flow chart has been removed.

<u>Part F Flow Chart</u>

This flow chart is entirely new.

<u>Part B, C, D, E *and F*: Follow-up</u>

This flow chart is now specific for Parts B, C, D, E, and F.

ECOG and physical exam procedures have been removed.

Tumor imaging has been added to the long term follow up visits.

The following footnotes have been added:

- Footnote 10: The same imaging technique should be used in a patient as used earlier in the study. In patients who discontinue study therapy early without documented disease progression, every effort should be made to continue monitoring their disease status by radiologic imaging. Monitoring should continue ~~(1) for approximately 6 months without disease progression,~~ (*1*) until

start of a new anti-cancer treatment, (*2*) until documented disease progression, or (*3*) until death, whichever occurs first.

- *Footnote 12: Patients who are complete response (CR) will continue to repeat Follow-Up Visit 2 every 3 months until either the end of the study or disease progression. If the patient experiences disease progression, patients will either enter the survival follow-up or have the option to be retreated with MK-3475 per the investigator's discretion except in the case of chemotherapy combination (patients in Part E) chemotherapy will not resume.*

- *Footnote 13: Collection of all AEs through the 30 day Safety Follow up Visit and SAEs through the 6 month follow up (through visit FU2). Drug-related AEs should be reported at any time.*

- *Footnote 14: Triplicate measurements for Part F patients.*

Section 2.1.1 Primary Objectives

3) To evaluate the extent of tumor response that correlates with the degree of biomarker positivity in the tumors of ipilimumab naïve patients treated with MK-3475 with the intent that the cut point for the PD-L1 assay will be explored and refined with tumor samples from ipilimumab-naïve MEL.

Hypothesis: We will be able to define a sub-population of ipilimumab-naïve MEL patients whose tumors express PD-L1. These patients will have a clinically meaningful tumor response compared to ipilimumab naïve MEL patients whose tumors do not express PD-L1.

4) To evaluate anti-tumor activity of MK-3475 in unselected MEL refractory to ipilimumab patients and MEL patients refractory to ipilimumab with PD-L1 expressing tumors.

Hypothesis: Single agent MK-3475 will show a clinically meaningful response rate (RR) or disease-control-rate (DCR) in unselected MEL patients refractory to ipilimumab, however single agent MK-3475 will show a more clinically meaningful response rate (RR) or disease-control-rate (DCR) in MEL patients refractory to ipilimumab with PD-L1 expressing tumors.

Section 2.1.2 Secondary Objectives

3) To investigate the relationship between candidate efficacy biomarkers and anti-tumor activity of MK-3475:

- To evaluate the correlation between PD-L1 expression levels and anti-tumor activity of MK-3475, *excluding ipi-refractory patients as stated in the primary objectives*.

Section 2.2 Patient Inclusion Criteria

1) In **Part B** of the study, patients must have a histological or cytological diagnosis of MEL with progressive locally advanced or metastatic disease that is not amenable to definitive local therapy with curative intent.

Ipilimumab-naïve Patients:

- Patients naive to ipilimumab may not have received more than 2 prior systemic treatment regimens for treatment of MEL. ~~One of them can be a BRAF inhibitor.~~

Ipilimumab-treated Patients:

The below criteria was moved to this section.

- *After the first 13 patients are enrolled, patients who have had ipilimumab may be enrolled, provided the following requirements are met.*

Ipilimumab-refractory Patients:

With Amendment 05 *and 06*, patients who have had ipilimumab may be enrolled, provided the following requirements are met (these patients are considered **ipilimumab-refractory**):

- Patients with BRAF V600~~E~~ mutant melanoma must have also been previously treated with a BRAF and/or MEK inhibitor.

In **Part D** of the study, patients must have a histological or cytological diagnosis of MEL with progressive locally advanced or metastatic disease that is not amenable to definitive local therapy with curative intent.

- Patients must be naive to ipilimumab and may not have received more than 2 prior systemic treatment regimens for treatment of MEL. One of them *may have included* a BRAF or MEK inhibitor.

In **Part E** of the study, patients must have a histologically-confirmed or cytologically-confirmed diagnosis of non-small cell lung cancer.

- ~~First-line eligible p~~*P*atient*s* must be ~~treatment-~~naïve to systemic treatment *for NSCLC.*
- *Patients' tumors must express PD-L1 as confirmed by a central vendor.*
- *Patients have tumor(s) amenable to biopsy.*
- ~~Second-line eligible patients will have experienced progression of locally advanced or metastatic NSCLC after one prior systemic platinum-containing~~

~~doublet antineoplastic regime (Adjuvant therapy will count as a regime if administered within 1 year before the relapse).~~

*In **Part F** of the study, patients must have a histologically-confirmed or cytologically-confirmed diagnosis of non-small cell lung cancer,*

- *Patient has non-squamous NSCLC.*
- *Patients' tumors must express PD-L1 as confirmed by a central vendor.*
- *Patients have tumor(s) amenable to biopsy.*
- *Patients in F-1 must be naive to systemic treatment for NSCLC (adjuvant therapy may not have been administered within 1 year of the relapse).*
- *Patients in F-2 have experienced progression of locally advanced or metastatic NSCLC after two or more prior systemic antineoplastic regimens (Adjuvant therapy will count as a regimen if administered within 1 year before the relapse).*
- *Patient has an estimated life expectancy of at least 12 weeks.*

2) Measurable disease:

- In Part B, C, D, ~~and~~ E, *and F* of the study, patients must have measurable disease as defined per irRC (Appendix 6.5):

5) Patient must have adequate organ function as indicated by the following laboratory values.

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1,500 /mcL
Platelets	≥100,000 / mcL
Hemoglobin	≥9 g/dL or ≥5.6 mmol/L– without qualifications
Renal	
Serum creatinine	≤1.5 X upper limit of normal (ULN)
Hepatic	
Serum total bilirubin	≤ 1.5 X ULN **OR**
	Direct bilirubin ≤ ULN for patients with total bilirubin levels > 1.5 ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 X ULN **OR** ≤ 5 X ULN for patients with liver metastases
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT)	≤1.5 X ULN *(Only if not using anticoagulants)*
Activated Partial Thromboplastin Time (aPTT)	≤1.5 X ULN *(Only if not using anticoagulants)*

6) Patient (Parts A, B, C, D, ~~and~~ E *and F*) has voluntarily agreed to participate by giving written informed consent. For Parts B, C, D, ~~and~~ E *and F,* patient has agreed to a fresh biopsy of tumor (that can be biopsied based on investigator's assessment) and to providing the acquired tissue for biomarker analysis. Tissue obtained for the biopsy must not be previously irradiated. *No systemic antineoplastic therapy may be received by the patient between the time of the biopsy and the first administration of MK-3475.*

9) Subject may also provide consent/assent for Future Biomedical Research. However, the subject may participate in the main trial without participating in Future Biomedical Research.

2.3 Patient Exclusion Criteria

9) ~~Patient has an active autoimmune disease or a documented history of autoimmune disease, except vitiligo or resolved childhood asthma/atopy.~~ *Patient has an active autoimmune disease or a documented history of autoimmune disease or syndrome that requires systemic steroids or immunosuppressive agents. Patients with vitiligo or resolved childhood asthma/atopy would be exception to this rule. Patients that require intermittent use of bronchodilators or local steroid injections would not be excluded from the study. Patients with hypothyroidism that is stable on hormone replacement will not be excluded from the study.*

10) ~~Patient had prior therapy with an anti-PD-1 antibody~~ *Patient had prior treatment with any other anti-PD-1, or PD-L1 or PD-L2 agent* or an antibody targeting other immuno-regulatory receptors or mechanisms (with exception of ipilimumab in study Part B and Part C).

2.4.1 Summary of Study Design

This is an open-label, Phase I study in patients with locally advanced or metastatic MEL, NSCLC, or carcinoma. The study has *6* parts.

Part B

Part B will only enroll patients with MEL. MK-3475 will be administered at 2 mg/kg and 10 mg/kg. The dosing interval to be used in Part B for patients who consent under protocol amendment 001-02 will be repeated Q2W. These patients will continue Q2W dosing until they discontinue study therapy. For patients consented under protocol amendments 001-03, 001-04, 001-05, *001-06*, or following approval of the administrative memo dated 06-Jan-2012, dosing will be Q3W. Study treatment will continue until disease progression, unacceptable toxicity, or the investigator considers it in the best interest of a patient to discontinue study therapy.

It is expected that Part B will enroll approximately *276* patients, including 76 ipilimumab-naïve patients: approximately 61 patients at 10 mg/kg; and 15 patients at 2 mg/kg. *Part B will also include* approximately 40 patients who had previously received

ipilimumab (at 10 mg/kg), and *80* patients who are ipilimumab refractory at 2 mg/kg and *80* patients who are ipilimumab refractory at 10 mg/kg. The first 13 patients enrolled in Part B will be required to be ipilimumab-naive.

Part E

Part E will enroll approximately *146* patients with NSCLC. *All patients must have tumors that express PD-L1 to be eligible for enrollment. In the carboplatin/paclitaxel* chemotherapy combination, *132* patients will be randomized *1:1:1*, manually by the Sponsor based on a computer-generated allocation schedule, to *2 mg/kg (44 patients), 5 mg/kg (44 patients), and 10 mg/kg (44 patients)* using an allocation schedule generated in-house. *In the cisplatin/pemetrexed chemotherapy combination, 14 patients will be enrolled at 10 mg/kg.* Once a patient is eligible for treatment, the Sponsor will inform the site of the appropriate dose to administer.

Initially *the carboplatin/paclitaxel* chemotherapy combination will enroll *18* patients simultaneously to evaluate DLTs. These patients will be randomly assigned to either 2 mg/kg (6 patients), *5 mg/kg (6 patients)* or 10 mg/kg (6 patients) of MK-3475. *The cisplatin/pemetrexed combination will also enroll 6 patients at 10 mg/kg of MK-3475*. All patients *in each combination at each dose* will then be evaluated for DLTs until completion of Cycle 1. Each MK-3475/chemotherapy combination may proceed independently from the other combination. Continued enrollment beyond these first patients in each combination will be according to dose continuation rules as defined in Section 3.2.5.4.7.

Radiological Tumor Assessment in Part E

For patients in Part E, following radiological tumor assessment at screening, the first radiological assessment of tumor response status will be performed at Week *6* (± 1 week), unless there is clinical indication warranting earlier radiologic imaging. The same imaging technique as used at baseline has to be used throughout the study.

If imaging at 6 weeks shows *complete response (CR) or partial response (PR) or* stable disease (SD), treatment will be continued and the next imaging studies will be conducted approximately at *Week 12*. Following *Week 12*, tumor imaging will be conducted approximately every 6 weeks subsequently.

If imaging at *6* weeks shows PD, it is at the discretion of the investigator to keep a patient on study treatment or to stop study treatment until repeat imaging will be repeated approximately 4 weeks later, in order to confirm PD. Patients that are deemed clinically unstable are not required to have repeat imaging for confirmation. This decision will be based on clinical judgment of a patient's overall clinical condition, including performance status, clinical symptoms, and laboratory data. If repeat imaging shows an objective response or stable disease relative to baseline, treatment with MK-3475 will continue/resume and the next imaging studies will be conducted approximately at Week

12, and every *6* weeks subsequently. If repeat imaging at Week *10* confirms PD, patients will be discontinued from study therapy.

Part F

Part F will enroll approximately 120 patients with NSCLC. All patients must have tumors that express PD-L1 to be eligible for enrollment. In F-1, 88 patients naïve to systemic treatment will be randomized 1:1, manually by the Sponsor based on a computer-generated allocation schedule, to 2 mg/kg (44 patients) and 10 mg/kg (44 patients) using an allocation schedule generated in-house. In F-2, 32 patients with 2 or more prior systemic treatments will be treated at 10 mg/kg. Once a patient is eligible for treatment, the Sponsor will inform the site of the appropriate dose to administer.

Radiological Tumor Assessment in Part F

The response criteria and patient management will follow the described principles and guidelines as per Part C.

Section 2.4.2 Definition of Dose-Limiting Toxicities

DLTs 2 to 6 have been renumbered to 3 to 7.

1. Grade 4 non-hematologic toxicity *(not laboratory)*.

2. *Grade 4 hematologic toxicity lasting ≥14 days.*

3. Grade 3 non-hematologic toxicity *(not laboratory)* lasting >3 days despite optimal supportive care.

    - ~~Grade 3 fatigue will NOT be classified as DLT, irrespective of duration.~~

If a patient experiences a DLT in Cycle 1, study therapy *may* be discontinued *following discussion and agreement between the Sponsor and Investigator. An alternative consideration may be dose modification of MK-3475 as described in Section 3.2.5.4.9 with continued therapy.*

Section 2.4.3 Treatment Plan

Table 2-1

Patient Distribution Table

	Amendment 001-02	Amendment 001-03/04	Amendment 001-05	*Amendment 001-06 (new)*	Total N
Part A Dose Escalation	N=10[1]				28 Solid Tumor
Part A-1	N=6[1]				
Part A-2		N=12 (Q3W)			
Part B (MEL)	**Ipilimumab naïve** at 10 mg/kg (Q2W)[2] N=46	**Ipilimumab naïve** at 10 mg/kg (Q3W) N=15			61
	Ipilimumab treated at 10 mg/kg (Q2W)[2] N=20	**Ipilimumab treated** at 10 mg/kg (Q3W) N=20			40
		Ipilimumab naïve at 2 mg/kg (Q3W) N=15			15
			Ipilimumab refractory at 10 mg/kg (Q3W) N=20	***Ipilimumab refractory*** *at 10 mg/kg (Q3W) N=60*	*80*
			Ipilimumab refractory at 2 mg/kg (Q3W) N=40	***Ipilimumab refractory*** *at 2 mg/kg (Q3W) N=40*	*80*
Part C (NSCLC)		10 mg/kg (Q3W) N=35			35
Part D (MEL)			**Ipilimumab naïve** at 2 mg/kg (Q3W) N=44		44
			Ipilimumab naïve at 10 mg/kg (Q3W) N=44		44

	Amendment 001-02	Amendment 001-03/04	Amendment 001-05	*Amendment 001-06 (new)*	Total N
Part E (NSCLC)				*1L: 2 mg/kg (Q3W) + carboplatin/ paclitaxel N=44*	*44*
				1L: 5 mg/kg (Q3W) + carboplatin/ paclitaxel N=44	*44*
				1L: 10 mg/kg (Q3W) + carboplatin/ paclitaxel N=44	*44*
				1L: 10 mg/kg (Q3W) + cisplatin/pemetrexed N=14	*14*
Part F (NSCLC)				*1L: 2 mg/kg (Q3W) N=44*	*44*
				1L: 10 mg/kg (Q3W) N=44	*44*
				3L+: 10 mg/kg (Q3W) N=32	*32*
	1L = First line arm *3L+ = Third line or greater arm* 1 The dosing interval between Cycle 1 and Cycle 2 is 28 days, Cycle 2 and beyond will be repeated every 14 days 2 Patients in Part B are dosed Q2W. Following approval of Amendments 001-03, 001-04, 001-05, *001-06*, or following approval of the administrative memo dated 06-Jan-2012, new patients will be dosed Q3W.				

Dose escalation in individual patients will not be permitted in this study, except as indicated for patients enrolled in Part A-2. In addition, for detailed guidelines for dose modifications ~~and treatment holidays~~, see Section 3.2.5.4.9~~ and 3.2.5.4.10 respectively~~. ~~Continuation of study therapy beyond 2 years will be contingent on the continued availability of MK-3475 drug product.~~

Section 2.7 Statistical Analysis Plan Summary

Efficacy Assessment

Part B ipilimumab-treated and ipilimumab-refractory, Part C, Part D, Part E *and Part F*: RR will be the primary endpoint for efficacy assessment. A 95% confidence interval for RR will be provided for each population. Although DCR is not the primary endpoint, similar analysis will also be provided.

In addition, Kaplan-Meier plots and descriptive statistics of progression-free-survival (PFS) and overall survival (OS) will be provided. Descriptive statistics will also be provided for analysis of response duration and tumor volumetric change. Further, the

95% confidence intervals will be provided for all the efficacy endpoints of interest between *two dose levels in Part B,* Part D, Part E *and Part F*.

Sample Size Calculations

Part B ipilimumab-treated: With 40 patients *treated at 10 mg/kg*, the study has approximately 92%/98% power to rule out a ≤5% *spontaneous* RR (null hypothesis) when the true RR is 20%/25% at the 5% type I error rate (one-sided). The corresponding powers are 75%/90% when sample size is 30 and 59%/78% when sample size is 20 at Q3W or Q2W.

Part B ipilimumab-refractory: With *approximately 80 ipilimumab-refractory patients at each dose level, the study has ~85% (or 96%) power to detect a 15% (or 20%) difference in RR between the two doses at the 10% type I error rate (one-sided) when the RR in the inferior arm is 10%. A p-value of 10% approximately corresponds to a 7% empirical difference in RR. The two dose levels will be collapsed for a pooled analysis (for overall population as well as for a subpopulation classified by the PD-L1 level) when the treatment difference is not statistically significant at the 10% level (one-sided). While the spontaneous RR is likely less than 5%, there is no historical data on response rate of chemotherapies in the ipilimumab-refractory population. However, it ranged from 5% to 10% for chemotherapies in three recently completed phase 3 studies (ipilimumab in 1st line and trametinib and vemurafenib in patients with BRAF V600E mutation). Therefore, it is reasonable to use 10% as the null hypothesis for testing the anti-tumor activity of MK-3475 against chemotherapies in this population. With 80 patients treated at a dose level, the study has 93% power to reject the null hypothesis at a type I error rate of 2.5% (one-sided) when the true response rate of MK-3475 is 25%. A p-value of 2.5% approximately corresponds to a 19% empirical response rate. With the prevalence of high PD-L1 projected to be from 40% to 60%, the number of high PD-L1 patients treated at a dose level ranges from 32 to 48 and the half-width of the 95% confidence intervals for RR at a dose level approximately ranges from 14% to 17% when the true RR is 50% and from 13% to 16% when the true RR is 70% or 30%. With 32 to 48 patients, the study has 79% to 94% power to reject the null hypothesis of 10% RR at type I error rate of 2.5% (one-sided) when the true RR is 30%.*

Part E NSCLC: *With 44 1L patients treated at a dose level, the study has 91% power to test the null hypothesis of RR=25% at 2.5% type I error rate (one-sided) when the true RR is 50%. A p-value of 2.5% approximately corresponds to an empirical RR of 41% (18/44). With 44 patients per dose level, the study has 85% power to detect a 25% difference in RR (i.e., 50% vs 25%) at alpha=10% (1-sided) between two dose levels. A P-value of 10% approximately corresponds to a 13% empirical difference in RR. The Cochran-Armitage method will be used for testing a linear trend in dose response at 10% (one-sided). With 44 patients at a dose level, the study has >80% power to detect a trend when the RRs are 30%, 40% and 50% from low dose to high dose. With 14 patients treated at 10 mg/kg in combination with cisplatin and pemetrexed,* the study has 90% power to rule out a ≥25% DLT rate if ≤ 1 patient develops a DLT *(i.e., probability of observing ≤ 1 DLT is 10% when true DLT rate is 25%)* or 92% power to rule out a ≥35%

DLT rate if ≤ 2 patients develop a DLT *(i.e., probability of observing ≤ 2 DLT is 8% when true DLT rate is 35%).*

Part F NSCLC: With 44 1L patients treated at a dose level, the study has 91% power to test the null hypothesis of RR=25% at 2.5% type I error rate (one-sided) when the true RR is 50%. A p-value of 2.5% approximately corresponds to an empirical RR of 41% (18/44). With 44 patients per dose level, the study has 86% power to detect a 25% difference in RR (i.e., 45% vs 20%) at alpha=10% (1-sided) between two dose levels. A P-value of 10% approximately corresponds to a 13% empirical difference in RR. With 32 3L+ patients treated at 10 mg/kg, the study has 90% power to test the null hypothesis of RR=10% at 2.5% type I error rate (one-sided) when the true RR is 35%. A p-value of 2.5% approximately corresponds to an empirical RR of 25% (8/32).

Section 3.1.4 Planned Exploratory Biomarker Research

Redacted

Section 3.1.5 Rationale for Future Biomedical Research

Redacted

Redacted

Section 3.2.2 Prohibited Medications

For patients enrolled in Part E, appropriate doses of corticosteroid for use as side effect prophylaxis that are considered standard of care for the particular cytotoxic chemotherapy accompanying MK-3475 are acceptable. It is not known what effect, if any, corticosteroid at these doses may have on the efficacy of MK-3475, *but unnecessary corticosteroid use should be avoided. Listed below in Table 3-2 are the appropriate doses of corticosteroid use for each chemotherapy.*

Table 3-2

Corticosteroid Prophylaxis with Chemotherapy Regimens

	Corticosteroid Use		
Chemotherapy Regimen	*1 Day Prior to Dose*	*Day of Dose*	*1 Day Post-Dose*
Carboplatin/Paclitaxel		*20 mg*	
Cisplatin/Pemetrexed	*4 mg bid*	*20 mg*	*4 mg bid*
Pemetrexed[1]	*4 mg bid*	*4 mg bid*	*4 mg bid*
[1] *Optional maintenance therapy*			

Section 3.2.5.1.2 Consent to Tumor Biopsy

Parts C, E *and F* will also investigate biomarkers in tumor tissue that may be able to identify which NSCLC patients have a high probability to benefit from treatment with MK-3475 and which do not. Thus a fresh tumor biopsy before start of study treatment is a mandatory requirement for participation in Parts C, E *and F*. Patients must give written consent before tumor biopsies. The most likely candidate biomarker (PD-L1) is most likely to be expressed later in the patient's disease course, thus a fresh sample will be needed to correlate with objective response or clinical benefit, rather than use an archival tissue block greater than two months old from the time of *first MK-3475 administration.*

Section 3.2.5.1.3 Consent and Collection of Specimens for Future Biomedical Research

The investigator or qualified designee will explain the Future Biomedical Research consent to the subject, answer all of his/her questions, and obtain written informed consent before performing any procedure related to the Future Biomedical Research sub-trial. A copy of the informed consent will be given to the subject.

Section 3.2.5.1.4 Future Biomedical Research

The following specimens are to be obtained as part of Future Biomedical Research:

- *Blood for genomics use*
- *Leftover Fresh Tumor Biopsy Tissue from the main study.*

Section 3.2.5.1.5 HLA Testing

Blood samples will be collected and HLA typing may be performed to determine if anti-tumor immune responses correlate to an individual's HLA alleles.

3.2.5.4.5 Electrocardiogram (ECG)

In Part A, a 12-lead ECG should be performed at Screening, at the Safety Follow-up Visit, and during study at the time points described in Section 1.7 (Study Flow Chart). In Part B, a 12-lead ECG should be performed at Screening, Cycle 1, and at the Safety Follow-up Visit. In Part C, a 12-lead ECG should be performed at Screening, Cycle 1, and at the Safety Follow-up Visit. In Part D, a 12-lead ECG should be performed at Screening, Cycle 1, Cycle 2, and at the Safety Follow-up Visit. *In Parts E and F, a 12-lead ECG should be performed at Screening and Cycle 1 (and Cycle 6 in Part F). Please refer to the Study Flow Chart for additional information.*

Section 3.2.5.4.6 Guidelines for Study Drug Administration

Patients in Part E will receive MK-3475 at 2 mg/kg, *5 mg/kg*, and 10 mg/kg, in combination with chemotherapy. The dosing interval will be every 3 weeks.

Patients in Part F will receive MK-3475 at 2 mg/kg and 10 mg/kg. The dosing interval will be every 3 weeks.

Section 3.2.5.4.7 Rules for Dose Escalation and Continuation

Rules for Part E Dose Continuation

DLTs observed in Cycle 1 only will be used to determine completion of the specific dose combination. Patients will initially be enrolled in a group of 6 for each dose level for a combination regimen. Following that initial safety assessment of DLTs in Cycle 1, provided few DLTs were observed, enrollment in that particular cohort may continue up to a maximum of 14 patients for the dose level in that combination regimen. If few DLTs were observed among those 14 patients, enrollment may proceed up to the maximum planned for that dose level for that combination regimen (MK-3475 at 2 mg/kg Q3W, 5 mg/kg Q3W, and 10 mg/kg Q3W in combination with carboplatin/paclitaxel - 44 patients each dose level, and MK-3475 at 10 mg/kg Q3W in combination with cisplatin/pemetrexed – 14 patients). Additionally patients will be observed for the late development (beyond Cycle 1) of significant toxicities that may be dose related which

may impact further study of a particular dose level in combination with cytotoxic chemotherapy. The dose continuance rules are as follows for each combination.

Carboplatin/paclitaxel:

- *An initial 18 patients with each combination are enrolled simultaneously. Patients are randomly assigned 1:1:1 to either 2 mg/kg (6 patients), 5 mg/kg (6 patients), or 10 mg/kg (6 patients).*
- *Following the randomization of the initial 18 patients for the combination, please consult the table below to determine the next steps. Find the number of DLTs experienced at each dose level for carboplatin/paclitaxel (Table 3-3).*

Table 3-3

Enrollment Instructions After 6 Patients Treated for 1 Cycle at Each Dose Level

Number of DLTs at each dose level of MK-3475 in combination with carboplatin/paclitaxel			***Subsequent Steps***
2 mg/kg	***5 mg/kg***	***10 mg/kg***	
≤ 1	*≤ 1*	*≤ 1*	*Randomize 1:1:1 up to 14 patients for dose levels 2, 5, and 10 mg/kg*
2-3	*≤ 1*	*≤ 1*	
≤ 1	*2-3*	*≤ 1*	
≥ 4	*≤ 1*	*≤ 1*	
≤ 1	*≥ 4*	*≤ 1*	
≤ 1	*≤ 1*	*2-3*	*Randomize 1:1 up to 14 patients for dose levels 2 and 5 mg/kg*
≤ 1	*≤ 1*	*≥ 4*	
2-3	*≤ 1*	*2-3*	
2-3	*≤ 1*	*≥ 4*	
≤ 1	*2-3*	*2-3*	*Finish enrolling up to 14 patients for 2 mg/kg*
2-3	*2-3*	*≤ 1*	
≤ 1	*2-3*	*≥ 4*	
2-3	*≥ 4*	*≤ 1*	
≥ 4	*2-3*	*≤ 1*	
≤ 1	*≥ 4*	*2-3*	
≥ 4	*≤ 1*	*2-3*	
≤ 1	*≥ 4*	*≥ 4*	
≥ 4	*≤ 1*	*≥ 4*	
≥ 4	*≥ 4*	*≤ 1*	*Terminate further enrollment in Part E*
2-3	*2-3*	*2-3*	
≥ 4	*2-3*	*2-3*	
2-3	*≥ 4*	*2-3*	
2-3	*2-3*	*≥ 4*	
2-3	*≥ 4*	*≥ 4*	
≥ 4	*2-3*	*≥ 4*	
≥ 4	*≥ 4*	*2-3*	
≥ 4	*≥ 4*	*≥ 4*	

Once 14 patients have been enrolled at the active dose levels being used in combination with carboplatin/paclitaxel, the following instructions regarding decisions based on DLT assessments should be used.

If dose levels 2, 5 and 10 mg/kg enrolled 14 patients then consult Table 3- for subsequent enrollment instructions.

Table 3-4

Enrollment Instructions After 14 Patients Treated for 1 Cycle at Each Dose Level

Number of DLTs at each dose level of MK-3475 in combination with carboplatin/paclitaxel			***Subsequent Steps***
2 mg/kg	***5 mg/kg***	***10 mg/kg***	
≤ 4	*≤ 4*	*≤ 4*	*Randomize 1:1:1 up to 44 patients for dose levels 2, 5, and 10 mg/kg (additional 30 patients per dose level)*
≥ 5	*≤ 4*	*≤ 4*	
≤ 4	*≤ 4*	*≥ 5*	*Randomize 1:1 up to 44 patients for dose levels 2 and 5 mg/kg (additional 30 patients per dose level)*
≤ 4	*≥ 5*	*≤ 4*	*Enroll up to 44 patients for dose level 2 mg/kg (additional 30 patients)*
≤ 4	*≥ 5*	*≥ 5*	
≥ 5	*≤ 4*	*≥ 5*	*Terminate further enrollment in Part E*
≥ 5	*≥ 5*	*≤ 4*	
≥ 5	*≥ 5*	*≥ 5*	

If only dose levels 2 and 5 mg/kg enrolled 14 patients then:

> *If ≤3/14 patients treated at 2 mg/kg and 5 mg/kg in combination with carboplatin/paclitaxel, then enroll 8 more patients at 10 mg/kg in combination with carboplatin/paclitaxel provided that ≤3/6 patients had DLTs at 10 mg/kg from the initial cohort. If 10 mg/kg is not a dose to be explored further, then randomize the next 60 patients between 2mg/kg and 5 mg/kg in a 1:1 fashion in combination with carboplatin/paclitaxel.*

If only dose level 2 mg/kg enrolled 14 patients, then:

> *If ≤3/14 patients treated at 2 mg/kg in combination with carboplatin/paclitaxel, then enroll 8 more patients at 5 mg/kg in combination with carboplatin/paclitaxel provided that ≤3/6 patients had DLTs at 5 mg/kg from the initial cohort. If 5*

mg/kg is not a dose to be explored further, then enroll the next 30 patients at 2mg/kg in combination with carboplatin/paclitaxel.

Additionally enrollment into the carboplatin/paclitaxel 2, 5 and 10 mg/kg dose levels of 44 patients each may be halted prematurely by the outcome of the planned interim analysis when 20 patients in each dose level have 3 months of follow up as described in Section 3.5.8.

Cisplatin/pemetrexed:

- *An initial 6 patients in the combination are enrolled to 10 mg/kg.*
- *Following the enrollment of the initial 6 patients for the combination regimen:*
    - *If ≤1/6 patients develops a DLT, enrollment of the remaining 8 patients will continue for the combination regimen.*
    - *If ≥2/6 patients experience a DLT, then further enrollment at the 10 mg/kg dose will be terminated, and enrollment of 6 patients into the next lower dose level may proceed (i.e 5mg/kg Q3W if started at 10 mg/kg, 2mg/kg Q3W if at 5mg/kg).*

Each combination may initially enroll, and subsequently continue or be terminated, independent of the other MK-3475/chemotherapy combinations. The highest dose to be tested is 10 mg/kg.

Section 3.2.5.4.8 Preliminary RP2D for Use in Parts B, C, D, E, *and F*

The dose to be used in Part C will be 10 mg/kg. The doses to be used in Parts D *and F*, will be 2 mg/kg and 10 mg/kg. *The doses in Part E to be used will be 2 mg/kg, 5 mg/kg and 10 mg/kg* in combination with chemotherapy.

Section 3.2.5.4.9 Guidelines for Dose Modifications

In case toxicity does not resolve to Grade 0-1 within 12 weeks after last administration of study drug, study therapy will be discontinued. With Investigator and Sponsor agreement, patients with a laboratory adverse event still at Grade 2 may continue in the study only if asymptomatic and controlled. In patients who continue on study therapy after experiencing such toxicity, if considered drug-related by the investigator, the dosing interval in subsequent cycles will be increased by 1 week (e.g., to 3 weeks in patients who were on an every 2 week schedule). *Following each dose delay due to toxicity, the dosing interval should increase by an additional week. For example, patients who began the study on a 3 week dosing schedule, and have stopped drug twice for due to a drug related toxicity, should now be dosing every 5 weeks. Patients in Part E who experience a DLT in Cycle 1 may consider an increase in the dose interval of MK-3475 by 1 week after consultation with the Sponsor, as opposed to discontinuing therapy completely. It should be noted that if the dose interval of MK-3475 is increased due to toxicity, the standard cytotoxic chemotherapy should continue to be administered per standard of care.*

For patients who experience a recurrence of the same severe AEs listed above with rechallenge of MK-3475, a consultation between the Sponsor and Investigator will occur to determine whether the patient should continue in the study.

~~Two dosing delays due to toxicity will be permitted. In the event of a third occurrence of a toxicity which would require dosing delay, study therapy will be discontinued permanently.~~

Guidelines for Part E

Patients in Part E who experience *an unacceptable* toxicity that is attributed to the chemotherapy in the investigator's opinion, may discontinue the cytotoxic chemotherapy, but may continue with MK-3475 until unacceptable toxicity or progression. *Dose reduction of the chemotherapy is also permitted, and should be executed per standard of care guidelines.*

Section 3.2.5.4.10 Treatment Holidays

This section was removed.

***Section 3.2.5.4.10* Supportive Care Guidelines**

- **Diarrhea**: Patients should be monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus). In symptomatic patients, infectious etiologies should be ruled out, and if symptoms are persistent and/or sever, endoscopic evaluation should be considered.
    - In patients with severe enterocolitis, MK-3475 *will be held* and treatment with systemic corticosteroids should be initiated at a dose of 1 to 2 mg/kg/day of prednisone or equivalent. When symptoms improve to Grade 1 or less, corticosteroid taper should be started and continued over at least 1 month.

- ***Events of Clinical Interest with a potential immunologic etiology (ECI-ie):*** *Please see the separate guidance document in the administrative binder regarding identification, evaluation and management of adverse experiences of a potential immunologic etiology. Depending on the type and severity of an ECI-ie, oral or intravenous treatment with a corticosteroid should be considered, in addition to appropriate symptomatic treatment of a given condition.*

Guidelines for Infusion Reactions

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

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

Section 3.2.5.4.10.2 Adverse Events *of Clinical Interest-Immune*

Events of clinical interest of a potential immunologic etiology (ECI-ie) may be defined as an adverse event of unknown etiology, associated with drug exposure and is consistent with an immune phenomenon. Efforts should be made to rule out neoplastic, infectious, metabolic, toxin or other etiologic causes prior to labeling an adverse event *of clinical interest*. Immunological, serological and histological (biopsy) data should be used to support the diagnosis of an immune-related toxicity. If an *ECI-ie* is noted, appropriate work-up (including biopsy if possible) should be performed.

Patients who develop a G2 or higher *ECI-ie* (e.g., colitis, skin rash, hepatitis, uveitis, hypo- or hyperthyroidism, hypophysitis, renal toxicity, pneumonitis, or any other), should be discussed immediately with the SPONSOR. Depending on the type and severity *of the event*, oral or intravenous treatment with a corticosteroid should be considered, in addition to appropriate symptomatic treatment of a given condition. *See the separate guidance document in the administrative binder regarding identification, evaluation and management of AEs of a potential immunologic etiology.*

Patients should be assessed for possible *ECI-ies* prior to each dose. Lab results should be evaluated and patients should be asked for signs and symptoms suggestive of an event. Patients who develop *ECI-ies* should have additional testing to rule out other etiologic causes. If lab results or symptoms indicated a possible *ECI-ie* then additional testing should be performed to rule out other etiologic causes. If no other cause was found, then it is assumed to be an *ECI-ie*.

Additional ECIs are described in Section 3.4.8.

Section 3.2.5.4.11 Duration of Therapy

- ~~Need for >2 dose delays due to toxicity as per the dose modification guidelines described in Section 3.2.5.4.9~~
- *Patients who have a confirmed complete response by two scans ≥ 4 weeks apart and who have been on MK-3475 treatment for at least 6 months may discontinue MK-3475 treatment at the discretion of the investigator after receiving at least two doses beyond the initial determination of CR. See Section 1.6.*

If a patient discontinues from the study, the procedures will be followed as described in *Section 3.2.3.4.12 and 3.2.3.4.13.*

~~Continuation of study therapy beyond 2 years will be contingent on the continued availability of MK-3475 drug product.~~

Section 3.2.5.4.12 Safety Follow-up Visit

After a patient is discontinued from study therapy (in Parts A, B, C, D, E, *and F*), a mandatory Safety Follow-Up Visit should be performed approximately 30 days after the last infusion of study medication. Procedures and assessments performed at the Safety Follow-Up Visit and beyond should follow the respective guidelines described in the Study Flow Chart (Section 1.7) for Parts A, B, C, D, E, *and F* as appropriate.

Section 3.2.5.4.13 Duration of Follow-up

In Parts B, C, D, E *and F*, patients who discontinued study therapy without documented disease progression, monitoring of their disease status by radiologic imaging should continue following the guidelines described in the Study Flow Chart (Section 1.7; Parts B, C, D, E *and F*: Follow-Up). Disease monitoring should continue ~~(1) for approximately 6 months without disease progression,~~ (*1*) until start of a new anti-cancer treatment *(information of the new cancer therapy will be collected),* (*2*) until documented disease progression, or (*3*) until death, whichever occurs first.

For patients in Parts A, B, C, D, E, and F who achieve a CR and who stop study treatment, the mandatory Safety Follow-Up Visit should be performed approximately 30 days after the last infusion of study medication. Procedures and assessments performed at the Safety Follow-Up Visit should follow the respective guidelines described in the Study Flow Chart as appropriate. Beyond the Safety Follow-Up Visit, patients will continue to be monitored for adverse events and followed per the standard follow-up period as described in the Study Flow Chart (Section 1.7). However, CR patients will not exit the standard follow-up, and will continue to return to the clinic every 3 months for the duration of the study following the Follow-Up flow chart.

Patients will be followed long-term for survival, as described in the Study Flow Chart (Section 1.7; Parts B, C, D, *E and F:* Follow-Up).

Section 3.2.5.5 Interim Data Locks

Part B

Additional interim analyses for Part C, D, E and F are described in Section 3.5.

Section 3.2.5.7 Withdrawal from Future Biomedical Research

Subjects may withdraw their consent for Future Biomedical Research and have their specimens and all derivatives destroyed. Subjects may withdraw consent at any time by writing to the principal investigator for the main trial. If medical records for the main trial are still available, the Investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@merck.com), and a form will be provided by

the Sponsor to obtain appropriate information to complete specimen withdrawal. Subsequently, the subject's specimens will be removed from the biorepository and be destroyed. A letter will be sent from the Sponsor to the investigator confirming the destruction. It is the responsibility of the Investigator to inform the subject of completion of destruction. Any analyses in progress at the time of request for destruction or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research trial data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main trial are no longer available (e.g., if the investigator is no longer required by regulatory agencies to retain the main trial records) or the specimens have been completely anonymized, there will no longer be a link between the subject's personal information and their specimens. In this situation, the request for specimen destruction cannot be processed.

Section 3.3.1.1 Response Criteria

For Parts A, B, C, D, E *and F*, tumor response will be determined by investigator assessment with retrospective independent central review.

In Part F, the irRC will also be applied as the primary measure for assessment of tumor response and as basis for all protocol guidelines related to disease status (e.g., discontinuation of study therapy). The irRC system is specifically described in the IIOM and in Appendix 6.5. RECIST 1.1 will be applied as a secondary measure. In addition, evaluation of volumetric tumor response will be performed by a central imaging vendor (see IIOM for details).

Section 3.3.1.2 Efficacy Endpoints

Part F

In Part F, the primary endpoint for NSCLC patients used to determine anti-tumor activity is RR. RR will include patients with CR or PR.

Secondary efficacy endpoints determined in Part F will include duration of response, PFS and OS. Duration of response will be measured from first documentation response to first documentation of disease progression. PFS will be measured from start of treatment to documentation of definitive disease progression as defined by irRC or death due to any cause, whichever occurs first. Survival will be measured from start of treatment to death due to any cause.

Section 3.3.1.3 Radiographic Assessments

In all patients (Parts A, B, C, D, E *and F*), baseline tumor imaging (CT or MRI, with a preference for CT) examinations must be performed within 30 days before enrollment. The same imaging technique as used at baseline has to be used throughout the study.

Part E

With the exception of imaging timelines (described below), the response criteria and patient management will follow the described principles and guidelines as per Part B.

For patients in Part E, following radiological tumor assessment at screening, the first radiological assessment of tumor response status will be performed at Week 6 (± 1 week), unless there is clinical indication warranting earlier radiologic imaging. The same imaging technique as used at baseline has to be used throughout the study.

If imaging at 6 weeks shows complete response (CR) or partial response (PR) or stable disease (SD), treatment will be continued and the next imaging studies will be conducted approximately at Week 12. Following Week 12, tumor imaging will be conducted approximately every 6 weeks subsequently.

If imaging at 6 weeks shows PD, it is at the discretion of the investigator to keep a patient on study treatment or to stop study treatment until repeat imaging will be repeated approximately 4 weeks later, in order to confirm PD. Patients that are deemed clinically unstable are not required to have repeat imaging for confirmation. This decision will be based on clinical judgment of a patient's overall clinical condition, including performance status, clinical symptoms, and laboratory data. If repeat imaging shows an objective response or stable disease relative to baseline, treatment with MK-3475 will continue/resume and the next imaging studies will be conducted approximately at Week 12, and every 6 weeks subsequently. If repeat imaging at Week 10 confirms PD, patients will be discontinued from study therapy.

Part F

In Part F, the response criteria and patient management will follow the described principles and guidelines as per Part C.

Section 3.3.2 Pharmacokinetic Measurements

Part F

In Part F, PK profile of MK-3475 will also be further characterized using a population modeling approach.

The time points for PK blood sampling are described in Section 1.7 (Part F Study Flow Chart).

Section 3.3.4 Biomarkers

Therefore, PD-L1 expression levels will be measured in MEL and NSCLC tumor tissues by immunohistochemistry (IHC) performed on tissue micro-arrays (TMAs). ~~The assay will utilize fluorescence labeling and computerized detection/quantification system to provide a more sensitive and continuous detection range and single numerical expression~~

~~index (i.e., combination of percent positivity and expression activity) rather than conventional IHC categorization.~~

If significant concordance is found between PD-L1 expression levels and antitumor activity *in tumors samples from patients with MEL who are ipilimumab naive*, then attempts will be made to estimate the PD-L1 cut-off *in this sub-population* which has the highest and/or lowest predictive value for ORR or DCR (at the 24 week landmark).

Section 3.4.8 Events of Clinical Interest

Following the guidelines described in Section 3.2.5.4.11.2, patients who develop a *G2* or higher *immune related ECI* (e.g., colitis, skin rash, hepatitis, uveitis, hypo- or hyperthyroidism, hypophysitis, renal toxicity, pneumonitis, or any other), should be discussed immediately with the SPONSOR and reported as an event of clinical interest. Depending on the type and severity of an *ECI*, oral or intravenous treatment with a corticosteroid should be considered, in addition to appropriate symptomatic treatment of a given condition.

3.5.3.1 Efficacy Endpoints

RR and DCR will serve as primary efficacy endpoints for the ipilimumab-naïve population in Part B of the study, and the study in this population is considered positive if the outcome in either endpoint is positive. The recently published immune-related response criteria (irRC) as *assessed by investigators* will be applied as primary measure for assessment of tumor response [18]. RR and DCR will be also assessed based on RECIST 1.1 *as supportive analyses*. Interim analyses will be based on RR and DCR at week 12. Confirmation is required for final analysis of RR, but not for the interim analyses

The primary endpoint is RR for Part B ipilimumab-treated, *Part B ipilimumab-refractory*, Part C, Part D, Part E *and Part F*. All other endpoints as defined above will serve as secondary endpoints.

3.5.4.1 Efficacy Analysis

The primary efficacy analyses will be based on the Full Analysis Set (FAS) population for each of the sub-populations (ipilimumab-naïve patients in Part B, ipilimumab-refractory patients in Part B, patients previously treated with ipilimumab in Part B, NSCLC patients in Part C, ipilimumab-naïve patients in Part D, NSCLC patients in Part E *and NSCLC patients in Part F*). Patients with measurable disease at baseline who received at least one dose of study treatment will be included in the FAS population.

The primary analyses of ipilimumab-refractory patients are based on patients who meet the definition of ipilimumab-refractoriness, irrespective of which amendment they are enrolled to. A subgroup analysis *of the ipilimumab-refractory patients* will be conducted for all patients randomized in Amendment 05 *and 06*.

3.5.4.2 Safety Analysis

The All Patients as Treated (APaT) population will be used for the analysis of safety data in this study. The APaT population consists of all patients who received at least 1 dose of study treatment in Part A, Part B, Part C, Part D, Part E *and Part F*.

3.5.4.4 Predictive Biomarker Analyses

The primary predictive biomarker analyses are based on subsets of the FAS population in Part B, Part C, Part D, Part E *and Part F* that includes patients with both a valid PD-L1 expression measurement and at least one disease assessment post-treatment. *Patients with MEL will be evaluated separately from patients with NSCLC. Different cut-point values may be applied to different tumor types. A cut-point for MEL will be explored and refined based on data from banked/purchased tumor tissues and in patients with ipilimumab-naïve MEL (Part B and/or D). This cut-point will be applied to patients with ipilimumab-refractory MEL (see Section 3.5.5.3 for details). Refinement of the cut-point for NSCLC will be explored based on data from banked/purchased tumor tissues and in patients from Part C and Part F.* Supportive analyses *will be* based on subsets of the *relevant* FAS populations that include patients with a valid PD-L1 expression measurement, irrespective of the availability of post-treatment disease assessments. In *these analyses*, those without post-treatment disease assessments will be imputed with the worst outcome in tumor response (see 3.5.5.4 for details).

3.5.5.1 Efficacy Analysis

Part B ipilimumab-treated, Part B ipilimumab-refractory, Part C, Part D, Part E *and part F*: RR will be the primary endpoint for efficacy assessment. A 95% confidence interval for RR will be provided for each population and by dose level as applicable. Although DCR is not the primary endpoint, similar analyses will also be provided.

In addition, Kaplan-Meier plots and descriptive statistics of progression-free-survival (PFS) and overall survival (OS) will be provided. Descriptive statistics will also be provided for analysis of response duration and tumor volumetric change. Further, the 95% confidence intervals will be provided for all the efficacy endpoints of interest in Part B, *Part C,* Part D, *Part E and Part F.*

Pharmacokinetic Analysis

MK-3475 PK variables (e.g., C_{max}, T_{max}, C_{trough} and AUC) will be calculated as appropriate and summary statistics will be provided. Graphical, non-compartmental and potentially exploratory compartmental analyses will be used for the analysis of the PK data. An exploratory analysis of a potential relationship between dose level, PK variables and clinical safety and anti-tumor activity will be performed as appropriate.

3.5.5.3 Predictive Biomarker Analysis *in MEL Patients*

To address the primary predictive biomarker hypothesis in the MEL population, the following three-step approach will be implemented: 1) testing the hypothesis that PD-L1 predicts tumor response in ipilimumab-naive patients; 2) estimation of cutoff point in ipilimumab-naive patients; 3) apply the cutoff point to analysis of ipilimumab-refractory patients. Since the cutoff point determination process is blinded to the ipilimumab-refractory population, the (pre-specified) retrospective analysis in this population has the necessary scientific rigor and integrity to potentially confirm a clinical benefit of MK-3475 in the "biomarker positive" patients.

Hypothesis testing: Kendall's tau statistic will be used for the primary predictive biomarker analysis *in ipilimumab-naive patients* [20]. The test statistics along with a one-sided p-value will be provided for testing the concordance between maximum total tumor volume reduction (%) produced by MK-3475 and PD-L1 expression levels in tumor tissue. Kendall's tau statistic is rank based. For the supportive analysis, those without a post-treatment disease assessment (presumably mainly due to discontinuation before week 12) will be assigned a lower rank (equivalent to less tumor reduction) than those with a post-treatment disease assessment. They will further be ranked by category of reasons for discontinuation (death, disease progression and other reasons) in ascending order, and among each category they will be ranked by time to discontinuation, the earlier the lower.

Estimation of cutoff point: All patients in this study are required to have new biopsies such that we expect the yield of tumor samples available for PD-L1 analysis to be very close to the number of patients enrolled. All tumors will be tested retrospectively, with the test operators blinded to all clinical data. Prior to testing in the ipilimumab-refractory patients, the scoring system and cutoff for the IHC assay will be determined using banked tumor samples and pretreatment biopsies from the ipilimumab-naive patients in this study whose treatment outcome is known. Four scoring systems will be evaluated initially: one based on H-score, the other three based on the percentage of tumor cells expressing PD-L1 with minimum intensities of 1+, 2+, and 3+, respectively. After a statistically significant concordance between PD-L1 score and maximum tumor volume change is established, receiver operating characteristic (ROC) analysis will be generated for each scoring system, and the one with the greatest area under the curve will be chosen. The cutoff will be chosen by statistical estimation assisted with visual inspection from the ROC. Finally, the following two confounding variables will be evaluated to determine whether or not they can be used to further improve the scoring system: staining pattern (diffuse versus regional) and mononuclear inflammatory infiltrate (absent versus PD-L1-negative infiltrate versus PD-L1-positive infiltrate). Subsequently, IPI-refractory samples will be sent to a third party contract research organization (CRO) for re-identification. The CRO will remove old identifying information from each sample and replace it with a new identifier. The samples will then be sent to the clinical laboratory sites for analysis. Thus, both Merck and the laboratories will be blinded to the linkage between PD-L1 test result and the clinical outcome. The

third-party CRO will release the key containing the old versus new identifiers to Merck only after database lock.

Application to ipilimumab-refractory population: Subgroup analyses will be conducted to compare DCR, RR and other efficacy endpoints between "biomarker positive" and "biomarker negative" ipilimumab-refractory populations determined by the cutoff point of PD-L1 expression level. A multivariate logistic regression analysis will be conducted to *further* assess the cutoff point *in this population* after adjustment of important baseline characteristics. Covariates in the regression model will include PD-L1 expression category ("biomarker positive" or "biomarker negative"), gender, age category (above or below median), ECOG performance status (0 or 1), LDH (≤ upper limit of the normal range OR > upper limit of the normal range or unknown), number of previous systemic therapies (< or ≥ median) and other prognostic factors and predictive biomarkers as appropriate. An estimate of treatment difference between the "biomarker positive" population and the "biomarker negative" population from the model, along with a nominal 95% confidence interval will be provided.

3.5.6 Multiplicity

The predictive biomarker hypothesis on *concordance between tumor volume change and* PD-L1 will be formally tested at a type I error rate of 2.5% (one-sided) separately for each part of the study, irrespective of the outcome from efficacy analyses. Once the null hypothesis is rejected, a step-down procedure may be applied to the testing of other biomarker hypotheses prospectively specified before the end of the study (in a separate document). While additional exploratory analyses will be conducted to evaluate alternative predictive biomarkers, there is no multiplicity control of such analyses and no formal conclusion can be made.

The efficacy hypothesis *on antitumor activity of MK-3475* is tested at 5% (one-sided) for Part B , at 10% (one-sided) for Part C and *Part D, and at 2.5% (one-sided) for Part E and Part F. Between-dose comparisons are all conducted at* 10% *(one-sided).*

Sample Size and Power Calculations

Part B ipilimumab-treated: With 40 patients *treated at 10 mg/kg*, the study has approximately 92%/98% power to rule out a ≤5% *spontaneous* RR (null hypothesis) when the true RR is 20%/25% at the 5% type I error rate (one-sided). The corresponding powers are 75%/90% when sample size is 30 and 59%/78% when sample size is 20 at Q3W or Q2W.

Part B ipilimumab-refractory: With 80 ipilimumab-refractory patients at each dose level, the study has ~85% (or 96%) power to detect a 15% (or 20%) difference in RR between the two doses at the 15% type I error rate (one-sided) when the RR in the inferior arm is 10%. A p-value of 10% approximately corresponds to a 7% empirical difference in RR. The two dose levels will be collapsed for a pooled analysis (for overall population as well as for a subpopulation classified by the PD-L1 level) when the treatment difference is

not statistically significant at the 10% level (one-sided).While the spontaneous RR is likely less than 5%, there is no historical data on response rate of chemotherapies in the ipilimumab-refractory population. However, it ranged from 5% to 10% for chemotherapies in three recently completed phase 3 studies (ipilimumab in 1st line and trametinib and vemurafenib in patients with BRAF V600E mutation). Therefore, it is reasonable to use 10% as the null hypothesis for testing the anti-tumor activity of MK-3475 against chemotherapies in this population. With 80 patients treated at a dose level, the study has 93% power to reject the null hypothesis at a type I error rate of 2.5% (one-sided) when the true response rate of MK-3475 is 25%. A p-value of 2.5% approximately corresponds to a 19% empirical response rate. With the prevalence of high PD-L1 projected to be from 40% to 60%, the number of high PD-L1 patients treated at a dose level ranges from 32 to 48 and the half-width of the 95% confidence intervals for RR at a dose level approximately ranges from 14% to 17% when the true RR is 50% and from 13% to 16% when the true RR is 70% or is 30%. With 32 to 48 patients in the PD-L1 high group, the study has 79% to 94% power to reject the null hypothesis of 10% RR at type I error rate of 2.5% (one-sided) when the true RR is 30%.Part C NSCLC: With 35 NSCLC patients treated at RP2D, the study has approximately 80% power to rule out a ≤9% RR (null hypothesis) when the true RR is 22% at the 10% type I error rate (one-sided).

Part D ipilimumab-naïve: With 44 patients treated at 2 mg/kg and 44 treated at 10 mg/kg, the study has 80% power to detect 30% vs. 10% or 90% power to detect 25% vs 5% in RR between the two dose levels at the 10% type I error rate (one-sided). A p-value of 10% approximately corresponds to a 12% empirical difference in RR.

Part E NSCLC: With 44 1L patients treated at a dose level, the study has 91% power to test the null hypothesis of RR=25% at 2.5% type I error rate (one-sided) when the true RR is 50%. A p-value of 2.5% approximately corresponds to an empirical RR of 41% (18/44). With 44 patients per dose level, the study has 85% power to detect a 25% difference in RR (i.e., 50% vs 25%) at alpha=10% (1-sided) between two dose levels. A P-value of 10% approximately corresponds to a 13% empirical difference in RR. The Cochran-Armitage method will be used for testing a linear trend in dose response at 10% (one-sided). With 44 patients at a dose level, the study has >80% power to detect a trend when the RRs are 30%, 40% and 50% from low dose to high dose. With 14 patients treated at 10 mg/kg in combination with cisplatin and pemetrexed, the study has 90% power to rule out a ≥25% DLT rate if a ≤ 1 patient develops a DLT (i.e., probability of observing ≤ 1 DLT is 10% when true DLT rate is 25%) or 92% power to rule out a ≥35% DLT rate if a ≤ 2 patients develop a DLT (i.e., probability of observing ≤ 2 DLT is 8% when true DLT rate is 35%).

Part F NSCLC: With 44 1L patients treated at a dose level, the study has 91% power to test the null hypothesis of RR=25% at 2.5% type I error rate (one-sided) when the true RR is 50%. A p-value of 2.5% approximately corresponds to an empirical RR of 41% (18/44). With 44 patients per dose level, the study has 86% power to detect a 25% difference in RR (i.e., 45% vs 20%) at alpha=10% (1-sided) between two dose levels. A P-value of 10% approximately corresponds to a 13% empirical difference in RR. With 32

3L+ patients treated at 10 mg/kg, the study has 90% power to test the null hypothesis of RR=10% at 2.5% type I error rate (one-sided) when the true RR is 35%. A p-value of 2.5% approximately corresponds to an empirical RR of 25% (8/32).

3.5.7 Subgroup Analyses and Effect of Baseline Factors

In assessment of anti-tumor activity in melanoma population, patients will be analyzed by treatment history with ipilimumab and by dose level and dosing interval (Q2W or Q3W). In addition, ipilimumab-naïve patients treated at 2 mg/kg Q3W and 10 mg/kg Q3W in Part B will be combined with those in Part D for a sensitivity analysis of treatment difference between the two doses. In assessment of anti-tumor activity in NSCLC populations *in Part C, Part E and Part F*, patients will be analyzed by line of therapy and by dose level.

3.5.8 Interim Analyses

Part B ipilimumab-naïve patients heading added.

The second planned interim analysis will be performed when all patients have completed tumor assessment at Week 12 *unless the primary objective of the analysis is not met earlier*. The primary purpose of this analysis is to provide an early assessment of overall anti-tumor activity, for administrative purpose (e.g., planning of a subsequent study in MEL). The focus of this analysis will be on ipilimumab-naïve patients. A Hochberg procedure with type I error rate of 5% (one-sided) will be applied to assist with the decision. Table 3-7 shows outcomes of interest that are on the borderline of the rejection zone of the null hypothesis, based on various hypothetical sample sizes of evaluable ipilimumab-naïve patients.

Part E and Part F NSCLC patients

For each dose combination with carboplatin and paclitaxel in Part E, an interim analysis will be conducted after the first 20 patients have had a 3-month follow-up. The accrual to a dose level may be put on hold if ≤6 patients have a response. The probability of observing ≤ 6 responses out of 20 patients is <10% when the true RR is 50%. With 20 patients, the study has approximately 75% power to detect a 25% difference (i.e., 50% vs 25%) at 10% type I error rate. Should accrual be put on hold, it will be resumed if the null hypothesis of RR=25% is rejected at 20% type I error rate (one-sided) based on all treated patients after they have a 4 -month follow-up (e.g., ≥ 10 responses out of 31 patients assuming 31 patients are enrolled before the accrual is put on hold). Totality of data including tumor volumetric change, disease control rate and safety will be reviewed before a decision on whether to resume the accrual is made.

For each dose level in Part F, an interim analysis will be conducted after the first 20 patients have had a 3-month follow-up. The accrual to a dose level may be put on hold if ≤2 patients have a response. The probability of observing ≤ 2 responses out of 20 patients is <10% when the true RR is 25%. After a review of totality of data including

SUMMARY OF CHANGES

PRIMARY REASON FOR THIS AMENDMENT:

The primary objectives of this amendment are the increase in sample size to Part B, the removal of Part E, and the modification and increase in sample size of Part F. These changes are primarily encompassed by the following:

Part B: Compare the safety profile and tolerability, as well as evaluate the clinical activity of, MK-3475 in patients receiving 10 mg/kg every 2 weeks (Q2W) versus every 3 weeks (Q3W).

Part E: Removal of all Part E text.

Part F: Compare the safety profile and tolerability, as well as evaluate the clinical activity of, MK-3475 in patients receiving 10 mg/kg every 2 weeks (Q2W) versus every 3 weeks (Q3W).

Implementation of these objectives necessitates the following changes to the protocol:

- Addition of 230 ipilimumab-naïve, treated, or refractory patients with melanoma in Part B.
- All aspects of Part E have been removed.
- Addition of 270 patients with NSCLC to Part F-2:
  - The non-squamous histology restriction has been removed
  - 20/270 in F-2 will be biomarker negative

OTHER CHANGES INCLUDED IN THE AMENDMENT:

Throughout the protocol, procedures have been separately listed for Part A, Part B, Part C, Part D and Part F. No changes were made to Part A or Part C in this amendment. Changes specific to the conduct of Part B, D and F are listed here.

In addition, typographical errors and inconsistencies were corrected throughout the document and are not listed here. Protocol sections that include changes relevant to Part A, Part B, Part C, Part D and Part F but do not impact study conduct of these Parts are not listed here (e.g., 1.3 Summary of Rationale, 3.1.2 Rationale for This Study, 3.1.3 Rationale for Dose) and should be reviewed in their entirety.

All guidance for Part E has been removed from each section of the protocol, however not all Part E deletions have been included in the Summary of Changes.

Section 1.2 Indication

For Part F, patients whose tumors express PD-L1 with a histologically or cytologically confirmed diagnosis of ~~non-squamous~~ non-small cell lung cancer (NSCLC) with progressive locally advanced or metastatic disease after *one* or more prior systemic treatment regimens or naïve to systemic treatment.

Section 1.3 Summary of Rationale

Redacted

Section 1.4 Summary of Study Design

In **Part B**, patients with MEL will be enrolled at the preliminary RP2D(s) to characterize the tolerability and safety profile of the dose, and for preliminary evaluation of anti-tumor activity in MEL. *Additionally, different doses and dosing schedules will be compared in a randomized fashion in patients with advanced melanoma.*

In **Part F-*1***, patients *without priory systemic therapy* whose tumors express PD-L1 with ~~non-squamous~~ NSCLC will be enrolled at 10 mg/kg *Q2W and 10 mg/kg Q3W* to characterize the tolerability and safety profile of MK-3475 monotherapy, and for preliminary evaluation of the dose and anti-tumor activity in NSCLC. *In Part F-2, patients with prior systemic therapy whose tumors express PD-L1 with NSCLC will be enrolled at 10mg/kg Q3W and 10 mg/kg Q2W to characterize the tolerability and safety profile of MK-3475 monotherapy, and for evaluation of the dose and anti-tumor activity in NSCLC. A small cohort of previously-treated patients with at least two lines of*

systemic therapy whose tumors do not express PD-L1 will be enrolled and treated at a dose of 10 mg/kg Q2W.

Section 1.5 Sample

A total of approximately *1047* eligible patients will be enrolled in this study, with approximately 28 patients in Part A, approximately *506* patients in Part B, approximately 35 patients in Part C, approximately 88 patients in Part D, and approximately *390* patients in Part F.

Part B will enroll approximately *506* patients distributed as described in Table 1-1:

Table 1-1

Patient Distribution in Part B

	10 mg/kg	2 mg/kg
Ipilimumab Naïve	61[1,3]	15[2,3]
Ipilimumab Treated	40[1,3]	0[3]
Ipilimumab Refractory	80[2,3]	80[2,3]
Ipilimumab Naïve or Treated	*230[1,4]*	
1 Includes patients with dosing schedules of Q2W and Q3W. 2 Dosing schedule is Q3W *3 Up through Amendment 001-06* *4 Amendment 001- 07*		

Enrollment of patients at 2 mg/kg who are naïve to ipilimumab in Part B will begin once all 10 mg/kg patients in Part B are enrolled up through Amendment 04. All patients enrolled after the approval of Amendment *03* or approval of the administrative memo dated 06-Jan-2012, will be dosed Q3W *with the exception of patients enrolled under Amendment 07.*

Enrollment of the first 13 patients.... *Upon approval of Amendment 07, Part B will enroll an additional 230 patients irrespective of prior ipilimumab status. This cohort will randomize approximately 115 patients at 10 mg/kg Q2W and 115 patients at 10 mg/kg Q3W who meet the Part B eligibility criteria as provided in the current amendment in a 1:1 fashion, manually by the Sponsor, based on a computer-generated allocation schedule.* If a patient is ipilimumab-refractory and BRAF V600E mutant, then one of the prior systemic treatment regimens must have included *an approved treatment for BRAF mutant melanoma (a BRAF and/or MEK inhibitor) if allocated under Amendment 07.*

In Part F, ~~approximately 348~~ *390* patients with metastatic or locally advanced NSCLC may be enrolled, and patients must have measureable disease (see Section 2.2 and Appendix 6.5).

In F-1 (treatment-naïve systemically), all patients' tumor tissue will be tested for expression of PD-L1, as determined by IHC, using a laboratory developed assay performed during Screening. Eighty-eight patients whose tumors express PD-L1, and are naïve to systemic treatment, will be randomized 1:1, manually by the Sponsor based on a computer-generated allocation schedule, to 10 mg/kg of MK-3475 at either Q2W or Q3W. An analytically validated assay PD-1L IHC assay will be used to determine the PD-L1 status of FFPE tumor samples.

In F-2 (previously-treated systemically), all patients' tumor tissue will be tested for expression of PD-L1, as determined by IHC, using a laboratory developed assay performed during Screening. Under Amendment 06, the first 32 patients whose tumors express PD-L1, have non-squamous NSCLC, and have received at least two prior lines of systemic therapy are eligible for treatment with MK-3475 at 10 mg/kg Q3W. Under Amendment 07, 250 additional previously-treated patients for NSCLC with at least one prior line of systemic therapy whose tumors express PD-L1 will be randomized 3:2, manually by the Sponsor based on a computer-generated allocation schedule, to either 10 mg/kg Q3W or 10 mg/kg Q2W of MK-3475. These patients in F-2 will be stratified by either weak or strong PD-L1 expression level. Enrollment of patients with weakly positive tumor expression of PD-L1 will be limited to approximately 50% of the Q2W and Q3W patient cohorts. Additionally, 20 patients who are PD-L1 negative and have received at least two prior lines of systemic therapy for NSCLC will be eligible to receive MK-3475 at 10 mg/kg Q2W. An analytically validated assay PD-1L IHC assay will be used to determine the PD-L1 status of FFPE tumor samples.

Enrollment into the F-1 and F-2 cohorts will occur concurrently.

Section 1.6 Dosage/Dosage Form, Route, and Dose Regimen

MK-3475 may be resumed *(Second Course treatment)* upon disease recurrence in these patients. See Section 3.2.5.4.13 for details regarding follow up for CR patients who discontinue treatment with MK-3475*, and section 3.2.5.4.14 for details regarding eligibility for second course treatment and Section 1.7 (Study Flow Chart) for details on procedures.*

In Part B, MK-3475 will be administered at the preliminary RP2D(s) as per Section 1.5. For patients who consent under protocol amendment 001-02, dosing will be repeated Q2W at 10 mg/kg. For patients consented under protocol amendments 001-03, 001-04, 001-05, 001-06, or following approval of the administrative memo dated 06-Jan-2012, dosing in Part B will be repeated Q3W at 2 mg/kg and 10 mg/kg. *Patients who consent under protocol amendment 07 will be randomized 1:1, manually by the Sponsor, to 10 mg/kg MK-3475 at either Q2W or Q3W, using an allocation schedule generated in-house..* Patients who initiate therapy on the 2 week schedule will not switch to the 3 week schedule, unless there is an adverse experience warranting such a reduction in schedule.

Part F will be split between treatment naïve patients (F-1) and patients with *at least 1* prior systemic regimen (F-2). Once the appropriate line of therapy is identified, *treatment-naive* patients *whose tumors express PD-L1* will be randomized 1:1 in F-1, manually by the Sponsor based on a computer generated allocation schedule, to either *10 mg/kg Q2W or 10 mg/kg* Q3W. *Under amendment 07, 20 previously treated patients with at least two prior lines of therapy whose tumors do not express PD-L1 will receive 10 mg/kg Q2W in F-2. All other patients in F-2 will randomized 3:2 manually by the Sponsor, to either 10 mg/kg Q3W or 10 mg/kg Q2W of MK-3475 using an allocation schedule generated in-house.*

Upon approval of Amendment 07, investigators have the option to provide patients with 10 mg/kg Q3W dosing if they enrolled in F-1 under Amendment 06 at 2 mg/kg Q3W.

Listed below are the MK-3475 treatment groups in Part F:

F-1:

- *NSCLC: Treatment naïve (first-line treatment – 88 total patients):*
  - *10 mg/kg MK-3475 Q2W, PD-L1 tumor expression (44 patients)*
  - *10 mg/kg MK-3475 Q3W, PD-L1 tumor expression (44 patients)*

F-2:

- *NSCLC: 1 or more Prior Systemic Treatments (250 total patients):*
  - *10 mg/kg, MK-3475 Q3W, PD-L1 tumor expression (150 patients)*
  - *10 mg/kg, MK-3475 Q2W, PD-L1 tumor expression (100 patients)*
- *NSCLC : 2 or more Prior Systemic Treatments (52 total patients)*
  - *10 mg/kg, MK-3475 Q3W, PD-L1 tumor expression (32 patients)*
  - *10 mg/kg MK-3475 Q2W, no PD-L1 tumor expression (20 patients)*

Section 1.7 Study Flow Chart

In Each Flow Chart

The term “Fresh" tumor biopsy has been changed to "Newly Obtained" tumor biopsy.

Part B: 2 Week Schedule Flow Chart

This flow chart is unchanged with the following exceptions:

- Addition of ECG testing at Cycle 9.

- Addition of HLA collection at Screening.

- Footnote 5: Electrocardiogram (12-lead ECG) should be performed at Screening, at the time of PK blood collection for PK (Cmax) within 30 minutes after the end of the first infusion of MK-3475 *(Cycle 1), Cycle 9* and at the mandatory Safety Follow-up visit. *Triplicate 12-lead ECG measurements should be collected at the pre-dose and post dose at Cycle 1, and only post dose at Cycle 9 (Cmax). Only 1 measurement is required at Screening.*

- Deleted Footnote 16.

- Footnote 18: *See Section 3.3.1.3.*

- Footnote 20: Collection of archival tumor tissue for purpose of biomarker analysis is strongly encouraged. *For patients enrolled with Amendment 07, collection of archival tumor tissue is mandatory*. Specific instructions for tissue collection and shipment are provided in the Procedures Manual. If the subject signs the Future Biomedical Research (FBR) consent, any leftover tissue that would ordinarily be discarded at the end of the main study will be retained for FBR, again providing the patient has signed the FBR consent.

- *Footnote 23: Collected in patients enrolled with Amendment 07.*

Part B: 3 Week Schedule Flow Chart

This flow chart is unchanged with the following exceptions:

- Addition of ECG testing at Cycle 6

- Removal of sample collection for cytokine/chemokine panels

- Footnote 5: Electrocardiogram (12-lead ECG) should be performed at Screening, at the time of PK blood collection for PK (Cmax) within 30 minutes after the end of the first infusion of MK-3475, *post-dose at Cycle 6,* and at the mandatory Safety Follow-up visit.

- Deleted Footnote 16.

- Footnote 20: Collection of archival tumor tissue for purpose of biomarker analysis is strongly encouraged. *For patients enrolled with Amendment 07, collection of archival tumor tissue is mandatory.* Specific instructions for tissue collection and shipment are provided in the Procedures Manual. If the subject signs the Future Biomedical Research (FBR) consent, any leftover tissue that would ordinarily be discarded at the end of the main study will be retained for FBR, again providing the patient has signed the FBR consent.

- Footnote 18: *See Section 3.3.1.3.*

Part C: 3 Week Schedule Flow Chart

Footnote 19: *See Section 3.3.1.3.*

Part D: 3 Week Schedule Flow Chart

This flow chart is unchanged with the following exceptions:

- Addition of ECG testing at Cycle 6
- Removal of sample collection for cytokine/chemokine panels
- Footnote 5: Electrocardiogram (12-lead ECG) should be performed at Screening, prior to dosing in Cycle 1, at the time of PK blood collection for PK (Cmax) within 30 minutes after the end of the first infusion of MK-3475, postdose in Cycle 2 *and Cycle 6*, and at the mandatory Safety Follow-up visit.
- Deleted Footnote 16.
- Footnote 18: *See Section 3.3.1.3.*

Part E: 3 Week Schedule Flow Chart

This flow chart has been deleted.

Part F: 3 Week Schedule

This flow chart is unchanged with the following exceptions:

- Screening period changed to -42 to -1 days from -28 to -1 days
- Removal of sample collection for cytokine/chemokine panels
- Pulmonary function test added to screening
- Added EGFR mutation and EML4_ALK translocation testing to screening.
- Footnote 5: Electrocardiogram (12-lead ECG) should be performed at Screening, prior to dosing in Cycle 1, at the time of PK blood collection for PK (Cmax) within 30 minutes after the end of the first infusion of MK-3475. Triplicate 12-lead ECG measurements should be collected at the pre-dose and post dose at Cycle 1 *(Cmax)* and *only post dose of Cycle 6 (Cmax).* Only 1 measurement is required at Screening.
- Deleted Footnote 16
- Footnote 18: *See Section 3.3.1.3.*

- *Footnote 23: Required at Screening for patients without source documentation demonstrating EGFR wild-type and without EML4-ALK translocation. Analysis will be performed by a central laboratory.*

- *Footnote 24: Results of tumor tissue analysis to determine of PD-L1 expression, EGFR status, and EML4-ALK status should be obtained prior to initiating other Screening procedures.*

- *Footnote 25: Collection of FEV1, FVC and DLCO.*

Part F: 2 Week Schedule

This flow chart is entirely new.

Part B, C, D, F: Follow-Up

This flow chart is unchanged with the following exceptions:

Footnote 10: *Radiographic imaging in the Survival Follow-Up may be performed as clinically indicated or per local standard of care.*

Footnote 14: Triplicate measurements for *Part B patients who are Q2W and initially consented under Amendment 001-07, and* Part F patients

Second Course Phase (all Parts) - 2 Week Schedule

This flow chart is entirely new.

Second Course Phase (all Parts) - 3 Week Schedule

This flow chart is entirely new.

Second Course Phase: Follow up

This flow chart is entirely new.

Section 2.1.1 Primary Objectives

5) To evaluate anti-tumor activity of MK-3475 in patients with NSCLC with at least one prior systemic therapy whose tumors express a high level of PD-L1.

Hypothesis: Single agent MK-3475 will show a clinically meaningful response rate (RR) patients with NSCLC with at least one prior systemic therapy whose tumors express a high level of PD-L1.

Section 2.1.2 Secondary Objectives

1) To evaluate the RR of unselected patients with MEL refractory to ipilimumab and MEL naïve to ipilimumab, patients with MEL refractory to ipilimumab and MEL naïve to ipilimumab whose tumors express PD-L1, and patients with NSCLC with at least one prior systemic therapy whose tumors express a high level of PD-L1, per RECIST 1.1 criteria.

4) To investigate the relationship between candidate efficacy biomarkers and anti-tumor activity of MK-3475:

- To evaluate the correlation between PD-L1 expression levels and anti-tumor activity of MK-3475 *in patients with melanoma*, excluding ipi-refractory patients as stated in the primary objectives, *and separately, non-small cell lung cancer*.

Section 2.1.3 Tertiary Objectives

1) To examine concordance between archival tumor tissues, formalin-fixed, paraffin-embedded tissue (FFPET) and ~~fresh~~ *newly obtained* frozen tumor tissue with respect to PD-L1 expression and other candidate efficacy biomarkers.

Section 2.2 Patient Inclusion Criteria

1) Part B – Ipilimumab-treated patients

- Unequivocal PD following a dose ~~within 6 months of the first dose~~ of ipilimumab

Ipilimumab-refractory Patients:

With Amendment 05~~ and,~~ 06, *and 07* patients who have had ipilimumab may be enrolled, provided the following requirements are met (these patients are considered **ipilimumab-refractory**):

- Received at least two doses of ipilimumab *(minimum dose of 3 mg/kg).*

- Progressive disease *after ipilimumab* will be defined ~~as increase in tumor burden >25% relative to nadir (minimum recorded tumor burden) which is confirmed by repeat assessment~~ according to irRC (Appendix 6.5). *The initial evidence of PD is to be confirmed by a second assessment, no less than four weeks from the date of the first documented PD, in the absence of rapid clinical progression* (this evaluation is based on investigator assessment; SPONSOR will collect imaging scans for retrospective analysis). ~~Progressive disease will be defined (investigator determination based on site radiology reading; SPONSOR will collect CT scans for retrospective analysis) no less than four weeks from the date of the first documented PD.~~ Once PD is

confirmed, initial date of PD documentation will be considered as the date of disease progression. ~~Tumor burden is defined by irRC (Appendix 6.5).~~

- ~~Full~~ *R*esolution of ipilimumab related AEs (including irAEs) back to *Grade 0-1* ~~baseline~~ and <10 mg/day prednisone or equivalent dose for irAEs for at least two weeks prior to first dose of study drug.

- Patients with BRAF V600mutant melanoma must have had a prior treatment regimen that includes *vemurafenib, dabrafenib, or other approved* BRAF and/or MEK inhibitor.

Part D

- Patients must be naive to ipilimumab and may not have received more than 2 prior systemic treatment regimens for treatment of MEL. ~~One of them may have included a BRAF or MEK inhibitor.~~

Part E

~~In **Part E** of the study, patients must have a histologically-confirmed or cytologically-confirmed diagnosis of non-small cell lung cancer.~~

- ~~Patients must be naïve to systemic treatment for NSCLC.~~

- ~~Patients' tumors must express PD-L1 as confirmed by a central vendor.~~

- ~~Patients have tumor(s) amenable to biopsy.~~

- ~~Patient has an estimated life expectancy of at least 12 weeks.~~

Part F

- ~~Patient has non-squamous NSCLC~~

- *Under amendment 07, patients in F must have a known EGFR mutation and ALK translocation status.*

    - *Patients in F-1 should be EGFR wild type and without ALK translocation.*

    - *Patients in F-2 may have an EGFR mutation or ALK translocation and participate in this study if they have documented progression of their NSCLC on the appropriate tyrosine kinase inhibitor (only erlotinib or gefitinib, or crizotinib, respectively) and have documented progression of their NSCLC on subsequent platinum doublet chemotherapy*

- *Randomized* patients *in F-1 and* ~~all~~ *patients in F-2* must *have* tumors *that* express PD-L1 as *determined* ~~confirmed~~ by a central vendor. *The exception is the 20 patients to be enrolled in F-2 whose tumors do not express PD-L1.*

- *Under amendment 06, patients in F-2 must have experienced progression of locally advanced or metastatic NSCLC after at least two prior systemic antineoplastic regimens (adjuvant therapy will count as a regimen if administered within 1 year before the relapse).*

- *Under amendment 07, patients in F-2 have experienced progression of locally advanced or metastatic NSCLC after at least one prior systemic antineoplastic regimen, at least one of which must have been a platinum-containing doublet (adjuvant therapy will count as a regimen if administered within 1 year before the relapse).*

- *Investigator-determined radiographic progression of NSCLC by RECIST 1.1 on the most recent prior therapy (and on a tyrosine kinase inhibitor if the patient has an EGFR mutation or ALK translocation) must be determined. The site's study team must have reviewed pre-trial images that are of diagnostic quality from at least 2 dates to confirm that radiographic progression has occurred per RECIST 1.1 following initiation of the prior therapy. Note, the imaging obtained during screening may be one of the dates reviewed. These pre-MK-3475 images should be submitted to the central imaging vendor for a possible retrospective analysis of this eligibility criterion. The central vendor will not be confirming eligibility prior to randomization.*
- *Those patients who have received prior thoracic radiation with a dose > 30 Gy must wait at least 26 weeks before the first dose of MK-3475.*

2) Measurable disease:

- In Part B, C, D~~, E~~ and F of the study, patients must have measurable disease as defined per irRC (Appendix 6.5):

    - Tumor mass: Must be accurately measurable in 2 perpendicular diameters, with both its longest diameter and its longest perpendicular must be greater than or equal to 10 mm or 2 times the axial slice thickness. Clinical lesions will only be considered measurable when they are superficial, such as skin or palpable lymph node. For *MEL* patients who are being screened for enrollment in Part B, ~~the ipilimumab refractory cohort~~ *after approval of Amendment 07,* clinical lesions alone will not be considered as sufficient for enrollment; there must be measurable disease evident on CT imaging.

5)

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1,500 /mcL
Platelets	≥100,000 / mcL
Hemoglobin	≥9 g/dL or ≥5.6 mmol/L[1] ~~without qualifications~~
Renal	
Serum creatinine	≤1.5 X upper limit of normal (ULN)
Hepatic	
Serum total bilirubin	≤ 1.5 X ULN **OR**
	Direct bilirubin ≤ ULN for patients with total bilirubin levels > 1.5 ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 X ULN **OR** ≤ 5 X ULN for patients with liver metastases
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT)	≤1.5 X ULN (Only if not using anticoagulants[2]
Activated Partial Thromboplastin Time (aPTT)	≤1.5 X ULN (Only if not using anticoagulants[2])
1 Criteria must be met without a transfusion within 4 weeks of the blood draw *2 If patient is receiving anticoagulants, then value must be within therapeutic range for the condition the patient is being treated for.*	

6) Patient (Parts A, B, C, D~~, E~~ and F) has voluntarily agreed to participate by giving written informed consent. For Parts B, C, D~~, E~~ and F, patient has agreed to a ~~fresh~~ *newly obtained* biopsy of tumor (that can be biopsied based on investigator's assessment) and to providing the acquired tissue for biomarker analysis. Tissue obtained for the biopsy must not be previously irradiated. No systemic antineoplastic therapy may be received by the patient between the time of the biopsy and the first administration of MK-3475. *An archival specimen, is mandatory to submit for Part B patients enrolled with Amendment 07; patients who do not have an available archival specimen can only be enrolled after discussion with the Sponsor.*

8) Female patients enrolled in the study, who are not free from menses for >2 years, post hysterectomy/oophorectomy, or surgically sterilized, must be willing to use either 2 adequate barrier methods *or* a barrier method plus a hormonal method of contraception to prevent pregnancy or to abstain from heterosexual activity throughout the study, starting with Visit 1 through ~~90~~ *120* days after the last dose of study therapy. Approved contraceptive methods include for example; intra uterine device, diaphragm with spermicide, cervical cap with spermicide, male condoms, or female condom with spermicide. Spermicides alone are not an acceptable method of contraception.

Male patients must agree to use an adequate method of contraception starting with the first dose of study drug through ~~90~~ *120* days after the last dose of study therapy.

Section 2.3 Patient Exclusion Criteria

1) Patient who has had chemotherapy, radioactive, or biological cancer therapy within 4 weeks prior to the first dose of study therapy, or who has not recovered to CTCAE grade 1 or better from the adverse events due to cancer therapeutics administered more than 4 weeks earlier. *Patient who has had erlotinib or gefitinib within 1 week prior to the first dose of study therapy, or who has not recovered to CTCAE Grade 1 or better from the adverse events due to either of these drugs administered more than 1 week earlier.*

4) Patient ~~is~~ *has a medical condition that requires* ~~on~~ chronic systemic steroid therapy or on any other form of immunosuppressive medication.

5) *Patient has risk factors for bowel obstruction or bowel perforation (including but not limited to a history of acute diverticulitis, intra-abdominal abscess, abdominal carcinomatosis).* ~~Patient has a history of acute diverticulitis, intra-abdominal abscess, GI obstruction, abdominal carcinomatosis which are known risks factors for bowel perforation~~

7) Patient has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Patients with previously treated brain metastases may participate provided they are clinically stable for at least ~~8~~ *4* weeks prior to study entry, have no evidence of new or enlarging brain metastases and are off steroids *for at least 7 days from the first dose of MK-3475*.

Part B MEL and Part F NSCLC patients who are entering the study under Amendment 07 careful consideration should be given to the possibly of asymptomatic brain metastasis.

9) Patient has a history of pneumonitis or interstitial lung disease

Numbering of the exclusion criteria 10 and higher increase by one number following the addition of criterion #9.

11) Patient had prior treatment targeting PD-1: PD-L1 axis or CTLA ~~with any other anti-PD-1, or PD-L1 or PD-L2 agent or an antibody targeting other immuno-regulatory receptors or mechanisms~~ (with the exception of ipiliumub in study Part B and Part C), *or was previously randomized in any MK-3475 trial.*

- Examples of such ~~antibodies include (but are not limited to) antibodies against IDO, PD-L1, IL-2R, GITR~~ *agents include (but are not limited to): Nivolumab (BMS-936558 MDX-1106 or ONO- 4538); Pidilizumab (CT011); AMP-224; BMS-936559 (MDX 1105); MPDL3280A (RG7446); and MEDI4736.*

Section 2.4.1 Summary of Study Design

Part A

Patients will be monitored for safety, anti-MK-3475 antibodies and efficacy throughout the study. If available and consented by participating patients, archived tumor tissue will be collected. In Part A, *newly obtained* tumor biopsies may be performed for biomarker analysis in select patients with readily accessible tumor lesions and who consent to the biopsies. Ideally, follow-up biopsy should be taken from the same tumor lesion as the baseline biopsy.

Part B

Part B will only enroll patients with MEL. MK-3475 will be administered at 2 mg/kg and 10 mg/kg. The dosing interval to be used in Part B for patients who consent under protocol amendment 001-02 will be repeated Q2W. These patients will continue Q2W dosing until they discontinue study therapy. For patients consented under protocol amendments 001-03, 001-04, 001-05, 001-06, or following approval of the administrative memo dated 06-Jan-2012, dosing will be Q3W. *Patients consented under protocol Amendment 07 will be administered 10 mg/kg at either Q2W or Q3W.*

It is expected that Part B will enroll approximately *506* patients, including 76 ipilimumab-naïve patients: approximately 61 patients at 10 mg/kg; and 15 patients at 2 mg/kg. Part B will also include approximately 40 patients who had previously received ipilimumab (at 10 mg/kg), *approximately* 80 patients who are ipilimumab refractory at 2 mg/kg *Q3W* and 80 patients who are ipilimumab refractory at 10 mg/kg *Q3W*. *Amendment 07 will enroll approximately 115 additional patients at 10 mg/kg Q2W and another 115 patients at 10 mg/kg Q3W irrespective of their prior ipilimumab status (i.e., ipilimumab naïve or previously treated).*

~~Radiological~~ Tumor Assessment in Part B

In general, response criteria and patient management will follow the recently described principles and guidelines for immunotherapies of solid tumors [18]. These irRC take into account the observation that some patients with MEL can have a transient tumor flare/*tumor progression* in the first few months after start of immunotherapy with subsequent disease response.

If imaging at 12 weeks shows PD, it is at the discretion of the investigator to keep a patient on study treatment or to stop study treatment until repeat imaging will be repeated approximately 4 weeks later, in order to confirm PD. Patients that are deemed clinically unstable are not required to have repeat imaging for confirmation. This decision will be based on clinical judgment of a patient's overall clinical condition, including performance status, clinical symptoms, and laboratory data. If repeat imaging shows an objective response or stable disease ~~relative to baseline~~, treatment with MK-3475 will continue/ resume and the next imaging studies will be conducted approximately at Week 24, and

every 12 weeks subsequently. If repeat imaging at Week 16 confirms PD, patients will be discontinued from study therapy.

Patients will be monitored regularly for safety, efficacy and anti-MK-3475 antibodies throughout the study, as per the guidelines in Section 1.7. *Newly obtained* tumor biopsies for biomarker analysis are mandatory prior to the first dose at baseline.

~~Radiological~~ Tumor Assessment in Part C

Patients will be monitored regularly for safety, efficacy and anti-MK-3475 antibodies throughout the study, as per the guidelines in Section 1.7. *Newly obtained* tumor biopsies for biomarker analysis are mandatory prior to the first dose at baseline.

~~Radiological~~ Tumor Assessment in Part D

Part F

Part F will enroll approximately *390* patients with NSCLC. All patients *in F-1 and most patients in F-2* must have tumors that express PD-L1 to be eligible for enrollment. In F-1, 88 patients *whose tumors express PD-L1 and are* naïve to systemic treatment will be randomized 1:1, manually by the Sponsor based on a computer-generated allocation schedule, to *10 mg/kg Q2W* (44 patients) and 10 mg/kg *Q3W* (44 patients) using an allocation schedule generated in-house. *Under Amendment 06, 32 patients whose tumors express PD-L1 and have had at least two prior lines of systemic therapy will be treated with MK-3475 at 10 mg/kg Q3W. Under Amendment 07,* in F-2, *an additional 250* patients with *1* or more prior systemic treatments will be treated, *150 at 10 mg/kg Q3W and 100 at 10 mg/kg Q2W. Patients will be randomized 3:2 and assigned to a treatment group manually by the Sponsor based on a computer-generated allocation schedule. These patients in F-2 will be stratified by either weak or strong PD-L1 expression level. Enrollment of patients with weakly positive tumor expression of PD-L1 will be limited to approximately 50% of the Q2W and Q3W patients cohorts. Furthermore, in F-2, twenty patients whose tumors do not express PD-L1 and have received at least two prior lines of systemic therapy will receive 10 mg/kg Q2W.* Once a patient is eligible for treatment, the Sponsor will inform the site of the appropriate dose to administer.

~~Radiological~~ Tumor Assessment in Part F

The response criteria and patient management will follow the described principles and guidelines as per Part C.

Section 2.4.3 Treatment Plan

Table 2-1

Patient Distribution

	Amendment 001-02	Amendment 001-03/04	Amendment 001-05	Amendment 001-06	Amendment 001-07 (new)	Total N
Part A Dose Escalation	N=10[1]					28 Solid Tumor
Part A-1	N=6[1]					
Part A-2		N=12 (Q3W)				
Part B (MEL)	**Ipilimumab naïve** at 10 mg/kg (Q2W)[2] N=46	**Ipilimumab naïve** at 10 mg/kg (Q3W) N=15				61
	Ipilimumab treated at 10 mg/kg (Q2W)[2] N=20	**Ipilimumab treated** at 10 mg/kg (Q3W) N=20				40
		Ipilimumab naïve at 2 mg/kg (Q3W) N=15				15
			Ipilimumab refractory at 10 mg/kg (Q3W) N=20	**Ipilimumab refractory** at 10 mg/kg (Q3W) N=60		80
			Ipilimumab refractory at 2 mg/kg (Q3W) N=40	**Ipilimumab refractory** at 2 mg/kg (Q3W) N=40		80
					Ipilimumab naïve, or treated *at 10 mg/kg Q2W or Q3W N=230*	*230*

Patient Distribution (Cont.)

	Amendment 001-02	Amendment 001-03/04	Amendment 001-05	Amendment 001-06	Amendment 001-07 (new)	Total N
Part C (NSCLC)		10 mg/kg (Q3W) N=35				35
Part D (MEL)			**Ipilimumab naïve** at 2 mg/kg (Q3W) N=44			44
			Ipilimumab naïve at 10 mg/kg (Q3W) N=44			44
Part F (NSCLC)				1L: *10 mg/kg (Q2W)* N=44		44[3]
				1L: 10 mg/kg (Q3W) N=44		44[3]
				3L+: 10 mg/kg (Q3W) N=32		32[3]
					3L+: 10 mg/kg (Q2W) N=20	*20*[4]
					2L+: 10 mg/kg (Q3W) N=150	*150*[3]
					2L+: 10 mg/kg (Q2W) N=100	*100*[3]

Patient Distribution (Cont)

	Amendment 001-02	Amendment 001-03/04	Amendment 001-05	Amendment 001-06	Amendment 001-07 (new)	Total N
1L = First line arm 2L+ = Second line or greater arm 3L+ = Third line or greater arm 1 The dosing interval between Cycle 1 and Cycle 2 is 28 days, Cycle 2 and beyond will be repeated every 14 days 2 Patients in Part B are dosed Q2W. With Amendments 001-03, 001-04, 001-05, 001-06, or following approval of the administrative memo dated 06-Jan-2012, new patients are dosed Q3W. 3 Patients' tumors express PD-L1 4 Patients tumors do not express PD-L1						

Section 2.7 Statistical Analysis Plan Summary

Key elements of the statistical analysis plan are summarized below; details are provided in Section 3.5 of the protocol. In particular, details on predictive biomarker analyses are provided in Section 3.5.5.4, sample size and power calculations are provided in Section 3.5.7, and interim analyses are provided in Section 3.5.9.

Section 2.7.1 Efficacy Analyses

Analysis populations

The primary efficacy analyses will be based on the Full Analysis Set (FAS) population. Patients with measurable disease at baseline, which is defined separately under investigator evaluation and central review, who received at least one dose of study treatment will be included in the FAS population. Analyses of PFS and OS are based on the APaT population that consists of all patients who received at least 1 dose of study treatment.

Efficacy endpoints and analysis methods

RR and DCR as assessed per irRC by investigators will serve as primary efficacy endpoints for the ipilimumab-naïve population treated at 10 mg/kg in Part B enrolled through Amendment 4, and the study in this population is considered positive (i.e., demonstration of proof-of-concept) if the outcome in either endpoint is positive. A 95% confidence interval along with a one-sided p-value for testing the null hypothesis based on the binomial distribution will be provided for each for the two primary endpoints: overall RR and overall DCR.

The primary endpoint is RR to further demonstrate the anti-tumor activity of MK-3475 in all other populations. The primary measure for assessment of tumor response is based on irRC by investigators and the secondary measure is based on RECIST 1.1 by blinded central reviewers. DCR, response duration and PFS based on both irRC and RECIST 1.1, and OS will serve as secondary endpoints. A 95% confidence interval for RR will be provided for each population and by dose/schedule as applicable. Although DCR is not the primary endpoint, similar analyses will also be provided. In addition, Kaplan-Meier plots and descriptive statistics of progression-free-survival (PFS) and overall survival (OS) will be provided. Descriptive statistics will also be provided for analysis of response duration and tumor volumetric change. Between-treatment comparisons will be conducted for all efficacy endpoints as appropriate to investigate the dose/schedule difference.

Section 2.7.2 Safety Analyses

The All Patients as Treated (APaT) population will be used for the analysis of safety data in this study. The APaT population consists of all patients who received at least 1 dose of study treatment.

In order for a patient to be considered evaluable for the analysis of DLT, the patient must have either had a DLT in Cycle 1 or had received at least 90% of the prescribed dose of MK-3475 in Cycle 1 and completed all safety evaluations up to and including at least 28 days after the first administration of MK-3475 without experiencing a DLT. A patient without a DLT will replaced if he/she did not adequately complete the evaluation period associated with the first cycle of study therapy (i.e., discontinue prematurely due to a reason unrelated to study therapy) or if that patient received <90% of the prescribed dose.

Section 3.1.4 Planned Exploratory Biomarker Research

Redacted

Section 3.2.4.2 Contraception

The 2 birth control methods can be 2 barrier methods *or* a barrier method plus a hormonal method to prevent pregnancy, used throughout the study starting with Visit 1 through *120* days after the last dose of study medication. Male patients enrolled in this study must also agree to use an adequate method of contraception starting with Visit 1 through *120* days after the last dose of study drug.

Section 3.2.5.1.1 *Consent and Collection of Specimens for Future Biomedical Research*

The investigator or qualified designee will explain the Future Biomedical Research consent to the subject, answer all of his/her questions, and obtain written informed consent before performing any procedure related to the Future Biomedical Research sub-trial. A copy of the informed consent will be given to the subject.

Section 3.2.5.1.2 *Future Biomedical Research*

The following specimens are to be obtained as part of Future Biomedical Research:

- *Blood for genomics use*
- *Leftover Tumor Biopsy Tissue from the main study.*

Section 3.2.5.4.2 Vital Signs

To the extent feasible, blood pressure will be taken on the same arm throughout the study. A large cuff should be used for obese patients. Patients must be resting in a sitting position for 10 minutes prior to obtaining vital signs. ~~If blood pressure is >150/100 in a patient without a history of hypertension, or increased >20 mmHg (diastolic) from baseline measurement in a patient with a previous history of hypertension, the assessment should be repeated in 10 minutes for confirmation.~~

Section 3.2.5.4.5 Electrocardiogram (ECG)

In Part A, a 12-lead ECG should be performed at Screening, at the Safety Follow-up Visit, and during study at the time points described in Section 1.7 (Study Flow Chart). *Under amendment 07, in* Part B, a 12-lead ECG should be performed at Screening, Cycle 1, *Cycle 6,* and at the Safety Follow-up Visit. *Those patients who initially consent under Amendment 07 and are dosed at Q2W in Part B will have a 12-lead ECG performed at Screening, Cycle 1, Cycle 9, and at the Safety Follow-up Visit. These EKGs for the 10 mg/kg Q2W schedule will be in triplicate, except for screening. Those patients who initially consent under Amendment 07 and are dosed at 10 mg/kg Q3W will have a singlet 12-lead ECG performed at screening, Cycle 1, and Cycle 6.* In Part C, a 12-lead ECG should be performed at Screening, Cycle 1, and at the Safety Follow-up Visit. *Under amendment 07, in* Part D, a 12-lead ECG should be performed at Screening, Cycle 1, Cycle 2, *Cycle 6*, *and at the Safety Follow-up Visit*. In Part F, a 12-lead ECG should be *performed in triplicate for Q3W dosing at Screening,* at Cycle 1, Cycle 6, and at the Safety Follow-up Visit. *In Part F, a 12-lead ECG should be performed in triplicate for Q2W dosing at Screening, at Cycle 1, Cycle 9, and at the Safety Follow-Up Visit. The EKGs for the 10 mg/kg Q3W schedule in F will be in triplicate, except for screening.* Please refer to the Study Flow Chart for additional information. *EKGs performed during a Cycle will be within 30 minutes after completing administration of MK-3475.*

When enough patients treated at 10 mg/kg Q2W from Parts B and F and Q3W from Part F have been enrolled that will permit exclusion that the upper bound of the 90% confidence interval for mean change in QTc from baseline to maximum steady state plasma concentration of MK-3475 is above 20 milliseconds, an analysis will be performed for each schedule. Based on the primary data from this study, the standard deviation of change in QTc from baseline is estimated to be 19.5 milliseconds. With 10/16/34 patients, the study has 90% power to meet the criterion if the true change from baseline is 0/5/10 milliseconds. The half-width of the 90% confidence interval for mean change is 7.2/5.9 milliseconds when the sample size is 20/30. When data from these analyses demonstrate that MK-3475 has a low likelihood of increasing the QTc interval, the rigorous collection of ECG data in triplicate at many time-points will discontinue and routine monitoring with singlet ECGs readings may resume. Sites will be notified via Administrative Memo of this change.

Section 3.2.5.4.6 Guidelines for Study Drug Administration

Patients in Part B will receive MK-3475 at the preliminary RP2D(s) determined in Part A. The dosing interval to be used in Part B for patients who consent under protocol amendment 001-02 will be repeated Q2W. These patients will continue Q2W dosing until they discontinue study therapy. For patients consented under protocol amendments 001-03, 001-04, 001-05, 001-06 or following approval of the administrative memo dated 06-Jan-2012, dosing will be Q3W. *Patients who consent under protocol Amendment 07 will receive 10 mg/kg MK-3475 with a dosing interval of either Q2W or Q3W.*

Patients in Part *F-1* will receive MK-3475 at 10 mg/kg *with a dosing interval of Q2W or Q3W. Patients in F-2 under Amendment 06 will receive 10 mg/kg with a dosing interval of Q3W, while F-2 patients enrolled under Amendment 07 will receive 10 mg/kg MK-3475 at dosing intervals of either Q2W or Q3W.*

Section 3.2.5.4.8 Preliminary RP2D for Use in Parts B, C, D and F

The dose to be used in Part C will be 10 mg/kg. The doses to be used in Parts D will be 2 mg/kg and 10 mg/kg, and 10 mg/kg in Part F. *Amendment 07 will also explore optimal dosing interval in Part B and Part F cohorts.*

Section 3.2.5.4.9 Guidelines for Dose Modifications

MK-3475 will be withheld for the following adverse reactions:

- Grade 2~~-3~~ fatigue *alone* does not require the withholding of study therapy

In addition, MK-3475 will be withheld for any of the following adverse events. Permanent discontinuation should be considered following discussion with the SPONSOR if any of the following Adverse Events Warranting Potential Dose Modification are experienced:

- Grade 2 **clinical *immune related*** adverse reactions which persist *without improvement* for >4 weeks
- Inability to reduce corticosteroid dose for immune-related adverse events to ≤*10* mg prednisone or equivalent per day

In case *a drug related* toxicity does not resolve to Grade 0-1 within 12 weeks after last administration of study drug, study therapy *discontinuation is recommended* ~~will be discontinued.~~

Section 3.2.5.4.10.1 Pneumonitis

Recommended treatment for symptomatic pneumonitis:

- Dose interruption of MK-3475 and steroid intervention for ≤Grade 2 with option to return to treatment if improves to Grade ≤1 ~~or resolves within 4 weeks~~.

Section 3.2.5.4.10.2 Adverse Events of Clinical Interest: Immune Related Adverse Events

An immune related adverse event (irAE) may be defined as an adverse event of unknown etiology, associated with drug exposure and is consistent with an immune phenomenon. Efforts should be made to rule out neoplastic, infectious, metabolic, toxin or other etiologic causes prior to labeling an adverse event of clinical interest. Immunological, serological and histological (biopsy) data should be used to support the diagnosis of an

immune-related toxicity. If an irAE is noted, appropriate work-up (including biopsy if possible) should be performed. Some immune related adverse events (irAEs) are considered Events of Clinical Interest (ECIs).

In the event a patient develops any of the following irAEs, a detailed narrative of the event should be reported as an ECI to the SPONSOR within 24 hours of the event:

- *Grade ≥3 diarrhea*
- *Grade ≥3 colitis*
- *Grade ≥2 pneumonitis*
- *Grade ≥3 hypo- or hyperthyroidism*

A separate guidance document has been provided entitled "MK-3475 Immune-Related Adverse Event Identification, Evaluation and Management Guidance for Investigators". This document can be found in the administrative binder and provides guidance regarding identification, evaluation and management of irAEs. Additional irAEs that are considered ECIs by the SPONSOR are identified in this guidance document and also need to be reported to the SPONSOR within 24 hours of the event.

Patients should be assessed for possible *irAE ECIs* prior to each dose. Lab results should be evaluated and patients should be asked for signs and symptoms suggestive of an event. Patients who develop *irAE ECIs* should have additional testing to rule out other etiologic causes. If lab results or symptoms indicated a possible *irAE ECI* then additional testing should be performed to rule out other etiologic causes. If no other cause was found, then it is assumed to be an *irAE ECI.*

Section 3.2.5.4.12 Safety Follow-up Visit

Patients who are eligible for retreatment with MK-3475 (as described in Section 3.2.5.4.14) may have up to two safety follow-up visits, one after the Treatment Period and one after the Second Course Phase.

Section 3.2.5.4.13 Duration of Follow-up

Subjects who are eligible to receive retreatment with MK-3475 according to the criteria in Section 3.2.5.4.14 will move from the follow-up phase to the Second Course Phase when they experience disease progression.

Section 3.2.5.4.14 Second Course Phase (Retreatment Period for Post-Complete Remission Relapse ONLY)

Patients may be eligible to receive MK-3475 in the Second Course Phase of this study if the study remains open and the patient meets the following conditions:

- *Stopped initial treatment with MK-3475 after attaining an investigator-determined confirmed CR according to irRC*

- *Was treated for at least 24 weeks with MK-3475 before discontinuing therapy*
- *Received at least two treatments with MK-3475 beyond the date when the initial CR was declared*
- *Experienced an investigator-determined progression after stopping their initial treatment with MK-3475*
- *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 2.2*
- *Female patient of childbearing potential should have a negative urine or serum pregnancy test within 72 hours prior to receiving retreatment with study medication.*
- *Female patients of childbearing potential should be willing to use 2 methods of birth control or be surgically sterile, or a barrier method plus a hormonal method of contraception to prevent pregnancy, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study medication (Reference Section 2.2). Patients of child bearing potential are those who have not been surgically sterilized or have been free from menses for > 2 years (see Section 2.2)*
- *Male patients 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 patient's participation for the full duration of the trial or is not in the best interest of the patient to participate, in the opinion of the treating investigator.*

Patients who restart treatment will be retreated at the dose and dose frequency they received upon initial treatment with MK-3475.

Section 3.3.1.1 Response Criteria

In Part B, the irRC *(investigator assessment)* will be applied as the measure for assessment of tumor response and as basis for all protocol guidelines related to disease status (e.g., discontinuation of study therapy). The irRC system is specifically described in the IIOM and in Appendix 6.5. RECIST 1.1 will *also* be applied as a measure *for assessment of tumor response.* In addition, evaluation of volumetric tumor response will be performed by a central imaging vendor (see IIOM for details).

In Part C, the irRC *(investigator assessment)* will also be applied as the measure for assessment of tumor response and as basis for all protocol guidelines related to disease status (e.g., discontinuation of study therapy). The irRC system is specifically described in the IIOM and in Appendix 6.5. RECIST 1.1 will *also* be applied as a measure *for*

assessment of tumor response. In addition, evaluation of volumetric tumor response will be performed by a central imaging vendor (see IIOM for details).

In Part D, the irRC *(investigator assessed)* will be applied as the measure for assessment of tumor response and as basis for all protocol guidelines related to disease status (e.g., discontinuation of study therapy). The irRC system is specifically described in the IIOM and in Appendix 6.5. RECIST 1.1 will *also* be applied as a measure *for assessment of tumor response*. In addition, evaluation of volumetric tumor response will be performed by a central imaging vendor (see IIOM for details).

In Part F, the irRC *(investigator assessment)* will also be applied as the measure for assessment of tumor response and as basis for all protocol guidelines related to disease status (e.g., discontinuation of study therapy). The irRC system is specifically described in the IIOM and in Appendix 6.5. RECIST 1.1 will *also* be applied as a measure *for assessment of tumor response*. In addition, evaluation of volumetric tumor response will be performed by a central imaging vendor (see IIOM for details).

Section 3.3.1.2 Efficacy Endpoints

Part B

RR and DCR will serve as primary efficacy endpoints for the ipilimumab-naïve population treated at 10 mg/kg in Part B enrolled through Amendment 4, and the study in this population is considered positive (i.e., demonstration of proof-of-concept in this population) if the outcome in either endpoint is positive. The primary endpoint is RR to further demonstrate the anti-tumor activity of MK-3475 in all other populations and dose/schedules in Part B. DCR, response duration, PFS and OS will serve as secondary endpoints.

Part C

In Part C*, the primary endpoint is RR. DCR, response duration, PFS and OS will serve as secondary endpoints.*

Part D

In Part D, the primary *endpoint is RR. DCR, response duration, PFS and OS will serve as secondary endpoints.*

Part F

In Part F, the primary *endpoint is RR. DCR, response duration, PFS and OS will serve as secondary endpoints.*

Section 3.3.1.3 Radiographic Assessment

Part F

The response criteria and patient management will follow the described principles and guidelines as per Part C.

Section 3.3.4 Biomarkers

Therefore, PD-L1 expression levels will be measured in MEL and NSCLC tumor tissues by immunohistochemistry (IHC) performed on *tumor* tissue *on glass slides* ~~micro-arrays (TMAs).~~

Therefore, PD-L1 expression levels will be measured in MEL and NSCLC tumor tissues by immunohistochemistry (IHC) performed on tumor tissue on glass slides. *Statistical details for the biomarker analyses are described in Section 3.5 (Statistical Analysis Plan).*

Section 3.4.5 Immediate Reporting of Adverse Experiences to the SPONSOR

Any serious adverse experience should be recorded and reported within 24 hours ~~or, at least, on the following working day~~ to the SPONSOR via facsimile (found in the administrative binder)

Section 3.4.5.1 Serious Adverse Events

Any serious adverse experiences, including death due to any cause *other than progression of the cancer under study*, which occurs to any subject/patient entered into this study or within *90* days following cessation of treatment *or the initiation of a new anticancer therapy, whichever is earlier,* whether or not related to the investigational product, must be reported within 24 hours to one of the individual(s) listed on the contact information page.

Section 3.4.8 Events of Clinical Interest

Following the guidelines described in Section 3.2.5.4.10.2, *certain irAEs should also be reported to the SPONSOR as ECIs.* Depending on the type and severity of an *ECI*, oral or intravenous treatment with a corticosteroid should be considered, in addition to appropriate symptomatic treatment of a given condition.

All ECIs should be reported to the SPONSOR within 24 hours or, at least, on the following working day to the SPONSOR via facsimile (documentation is found in the Administrative Binder).

Section 3.4.9 Protocol-Specific Exceptions to Serious Experience Reporting

All untoward events, including suspected efficacy endpoints/endpoints events will be recorded in the their respective appropriate modules of the eCRF, and all requested information will be provided, including notation of whether or not the event meets the definition of "serious" provided in the protocol. If a suspected efficacy endpoint/endpoint event is determined to result in hospitalization or death, however, it will not be reported to the Sponsor as described in Section 3.4.5. Immediate Reporting of Adverse Experiences to the Sponsor except as follows:

A serious and unexpected adverse experience occurs for which there is evidence suggesting a causal relationship between the drug and the event, the event must also be reported as a serious and unexpected suspected adverse reaction within 24 hours to the Clinical Monitor either by electronic media or paper even if it is a component of the study endpoint (e.g., all-cause mortality).

Specifically, the suspected/actual events (as opposed to endpoints or endpoint components) covered in this exception are as follows: hospitalization or death due to progression of the cancer under study. Note: As described in section 3.4.5.1, any secondary primary cancer needs to be reported as an SAE.

For this protocol, the Following MedDRA Preferred Terms are considered suspected efficacy endpoint/endpoint events:

- *Disease Progression*
- *Malignant Neoplasm Progression*

The Sponsor will monitor unblinded aggregated efficacy endpoint event and other safety data including fatal events to ensure the safety of the subjects in the trial. Any hospitalization or fatal event 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.

Section 3.5.1 Responsibility for Analysis/In-Houe Blinding

This trial is being conducted as an open-label study (i.e., patients, investigators, and SPONSOR personnel will be aware of patient treatment assignments after each patient is enrolled and treatment is assigned). *However, for those randomized cohorts, treatment assignment is based on an allocation schedule generated in-house to maintain randomness.*

Section 3.5.3.1 Efficacy Endpoints

RR and DCR will serve as primary efficacy endpoints for the ipilimumab-naïve population *treated at 10 mg/kg in Part B enrolled through Amendment 4,* and the study in

this population is considered positive *(i.e., demonstration of proof-of-concept in this population)* if the outcome in either endpoint is positive. The recently published immune-related response criteria (irRC) as assessed by investigators will be applied as primary measure for assessment of tumor response [18]. RR and DCR will be also assessed based on RECIST 1.1 *by blinded central reviewers* as supportive analyses. Interim analyses will be based on RR and DCR at Week 12. Confirmation is required for final analysis of RR, but not for the interim analyses.

Secondary efficacy endpoints for the *above* population will include duration of response, progression-free survival (PFS) and overall survival (OS).

The primary endpoint is RR *to further demonstrate the anti-tumor activity of MK-3475 in all other populations. The primary measure for assessment of tumor response is based on irRC by investigators and the secondary measure is based on RECIST 1.1 by blinded central reviewers. DCR, response duration and PFS based on both irRC and RECIST 1.1, and OS* will serve as secondary endpoints.

Section 3.5.4.1 Efficacy Analysis

The primary efficacy analyses will be based on the Full Analysis Set (FAS) population. Patients with measurable disease at baseline, *which is defined separately under investigator evaluation and central review*, who received at least one dose of study treatment will be included in the FAS population. *Analyses of PFS and OS are based on the APaT population that consists of all patients who received at least 1 dose of study treatment.*

Section 3.5.4.4 Predictive Biomarker Analysis

The primary predictive biomarker analyses are based on *evaluable* patients with both a valid PD-L1 expression measurement and at least one disease assessment post-treatment. Patients with MEL will be evaluated separately from patients with NSCLC. Different *cutoff* points may be applied to different tumor types.

Section 3.5.5.1 Efficacy Analysis

Part B ipilimumab-naïve *treated at 10 mg/kg enrolled through Amendment 4*: Overall response rate (RR) and disease control rate (DCR) will be used as primary endpoints for efficacy assessment of the ipilimumab-naïve patients. A 95% confidence interval along with a one-sided p-value for testing the null hypothesis based on the binomial distribution will be provided for each for the two primary endpoints: overall RR and overall DCR. Similar analyses will be provided for interim analyses of RR and DCR at week 12. Exploratory analyses will be conducted to compare the PFS rate at 6-month and OS rate at 1-year with historical control as well as with the recent ipilimumab data adjusted with baseline factors such as ECOG [75].

RR will be the primary endpoint for efficacy assessment *in all other populations*. A 95% confidence interval for RR will be provided for each population and by dose/schedule as applicable. Although DCR is not the primary endpoint, similar analyses will also be provided. In addition, Kaplan-Meier plots and descriptive statistics of progression-free-survival (PFS) and overall survival (OS) will be provided. Descriptive statistics will also be provided for analysis of response duration and tumor volumetric change. *Between-treatment comparisons will be conducted for all efficacy endpoints as appropriate to investigate the dose/schedule difference*.

Section 3.5.5.4 Predictive Biomarker Analyses

MEL Patients

To address the primary predictive biomarker hypothesis in the MEL population, the following *two*-step approach will be implemented: *1) estimation of a cutoff point for PD-L1 expression level based on a training set of melanoma patients, and 2) application of the cutoff point to prospectively test the biomarker hypothesis (i.e., formal validation of the cut-point). The training set consists of patients from the cohort B enrolled through Amendment 04, including 20 ipi-naïve patients at 2 mg Q3, 22 ipi-naïve patients at 10 mg Q3, 41 ipi-naïve patients at 10 mg Q2, 32 ipi-treated patients at 10 mg Q3, and 16 ipi-treated patients at 10 mg Q2. Once the cutoff point is estimated, it will be applied to the analysis of* of randomized patients in Part B and Part D.

The cutoff point determination process is blinded to the validation analyses to ensure they have the necessary scientific rigor and integrity to confirm a clinical benefit of MK-3475 in the "biomarker positive" patients.

Estimation of cutoff point

All patients in the training set are required to have new biopsies such that we expect the yield of tumor samples available for PD-L1 analysis to be very close to the number of patients enrolled. All tumors will be tested retrospectively, with the test operators blinded to all clinical data. Four scoring systems will be evaluated initially: one based on H-score, the other three based on the percentage of tumor cells expressing PD-L1 with minimum intensities of 1+, 2+, and 3+, respectively. The latter two scoring systems (percentage of tumor cells with minimum intensities of 2+ or 3+) may be abandoned if the operators determine that they are too difficult to score.

Kendall's tau statistic along with a one-sided p-value will be provided for testing the concordance between maximum total tumor volume reduction (%) produced by MK-3475 and PD-L1 expression levels in tumor tissue [20]. Kendall's tau statistic is rank based. For the supportive analysis, those without a post-treatment disease assessment (presumably mainly due to discontinuation before week 12) will be assigned a lower rank (equivalent to less tumor reduction) than those with a post-treatment disease assessment. They will further be ranked by category of reasons for discontinuation (death, disease progression by RECIST 1.1 per central review and other reasons) in ascending order,

and among each category they will be ranked by time to discontinuation, the earlier the lower. Supportive analysis will be performed assessing the concordance between response by RECIST 1.1 per central review and PD-L1 expression.

Receiver operating characteristic (ROC) analysis will be generated for each scoring system. The cutoff point will be chosen by statistical estimation of Youden Index assisted with visual inspection from the ROC. In addition, the following two confounding categorical variables will be evaluated to determine whether or not they can be used to further improve the scoring system: "stroma pattern" (presence or absence of a band mononuclear inflammatory cells expressing PD-L1, in the stroma adjacent to tumor nests) and "dendritic pattern" (presence or absence of a lattice of dendritic cells expressing PD-L1, within tumor nests). Once the final scoring system and cutoff point is chosen, it will be documented before validation can be conducted.

Validation

Tumor samples from patients in the validation sets will be sent to a third party contract research organization (CRO) for re-identification. The CRO will remove old identifying information from each sample and replace it with a new identifier. The samples will then be sent to the clinical laboratory sites for analysis. Thus, both Merck and the laboratories will be blinded to the linkage between PD-L1 test result and the clinical outcome. The third-party CRO will release the key containing the old versus new identifiers to Merck only after database lock.

Patients with PD-L1 expression level above the final cutoff point will be analyzed by dose/schedule, separately for the ipi-refractory population and the ipi-naïve population. Based upon current data from this trial indicating similar response rates between ipi-naïve and ipi-treated patients, an analysis will also be performed where the two populations are combined for a given dose/schedule or even across doses/schedules as appropriate. RR, DCR and other efficacy endpoints will all be compared by PD-L1 expression category (above or below cutoff). A multivariate logistic regression analysis will be conducted to further assess the cutoff point after adjustment of important baseline characteristics. Covariates in the regression model will include PD-L1 expression category (above or below cutoff), gender, age category (above or below median), ECOG performance status (0 or 1), LDH (≤ upper limit of the normal range OR > upper limit of the normal range or unknown), baseline tumor volume (above or below median), number of previous systemic therapies (< or ≥ median) and other prognostic factors and predictive biomarkers as appropriate.

Part F 2L+ Patients

The randomization of the 250 2L+ patients may be stratified by PD-L1 expression level based on a preliminary cutoff point once available, mainly based on Part C data. Data based on the patients enrolled in the non-randomized portions of Part F will be pooled with Part C data, some data from Part A, and possibly data from 1L patients in Part F, to determine the final cutoff point for patients with strongly positive tumors (the primary

population in this cohort) using the same estimation methods as for the melanoma patients. Just like for the melanoma patients, the cutoff point is determined in isolation to the 250 patients enrolled in the randomized portion of Part F to ensure that the subgroup analysis of the patients with strongly positive tumors is blinded to the determination process. Notice that the cutoff point is driven by patients on the Q3W schedule. To properly compare the difference (if any) in cutoff point between the two dose schedules, patients treated at 10 mg/kg Q2W will be divided into two sets with half in the training set and half in the validation set for estimation and validation of a cutoff point specifically for the Q2W schedule.

Enrollment of patients with weakly positive tumors will be capped at 50%. Besides, an interim analysis will be conducted to potentially exclude patients with weakly positive tumors (based on final cutoff point) from further enrollment (see Section 3.5.9 for details). Regardless, the final cutoff point, once determined, won't be changed for the primary analysis purposes to maintain the integrity of the analysis.

Section 3.5.6 Multiplicity

A Hochberg procedure will be applied to final analysis of the two primary efficacy endpoints (RR and DCR) based on the ipilimumab-naïve *patients treated at 10 mg/kg in Part B enrolled through Amendment 4.* . The overall type I error rate is set at 5% (one-sided), i.e., the trial is considered to have reached the efficacy objective if the two corresponding p-values for testing the null hypothesis (RR=10% and DCR=30%) are less than 5% OR either one is less than 2.5%. There are two *planned* interim analyses for administrative purposes.

The efficacy hypothesis on anti-tumor activity of MK-3475 is tested at 5% (one-sided) for Part B *ipilimumab-treated* (non-randomized), at 10% (one-sided) for Part C, and at 2.5% (one-sided) for *all other populations*. Between-*dose* comparisons are all conducted at 20% (two-sided), *or equivalent 10% (one-sided) for sample size and power calculation purpose below*, except for Part B (10 mg/kg Q3W vs 10 mg/kg Q2W) which is conducted at 5% (two-sided).

Section 3.5.7 Sample Size and Power Calculations

Part B ipilimumab-naïve *enrolled through Amendment 4 (non-randomized)*

With 61 ipilimumab-naïve patients treated at t*he 10 mg/kg in both Q2W and Q3W*, the study has approximately 97% power to detect an effect size of RR=25% or DCR=50% under the null hypothesis of RR=10% and DRC=30%, or >99% power to detect an effect size of RR=30% or DCR=55%, at a type I error rate of 5% (one-sided) based on the Hochberg procedure. For the subgroup of patients on *a dose /schedule*, the corresponding powers to the two effect sizes are respectively 87% and 97% when the sample size is 40, 76% and 91% when the sample size is 30, and 44% and 62% when the sample size is 15.

Part B ipilimumab-treated *enrolled through Amendment 4 (non-randomized)*

With 40 patients treated at 10 mg/kg, the study has approximately 92%/98% power to rule out a ≤5% spontaneous RR (null hypothesis) when the true RR is 20%/25% at the 5% type I error rate (one-sided). With true RR assumed to be 20%/25%, the corresponding power is 75%/90% when sample size is 30 and 59%/78% when sample size is 20 at Q3W or Q2W.

Part B ipilimumab-refractory *enrolled after Amendment 04 (randomized: 10 mg/kg Q3W vs 2 mg/kg Q3W)*

With 80 ipilimumab-refractory patients at each dose level, the study has ~85% (or 96%) power to detect a 15% (or 20%) difference in RR between the two doses at the 10% type I error rate (one-sided) when the RR in the inferior arm is 10%. A p-value of 10% approximately corresponds to a 7% empirical difference in RR.

In addition to detecting dose response, we are also interested in testing whether MK-3475 is superior to putative chemotherapies in this population. While the spontaneous RR is likely less than 5%, there is no historical data on response rate of chemotherapies in the ipilimumab-refractory population. However, it ranged from 5% to 10% for chemotherapies in three recently completed phase 3 studies (ipilimumab in 1st line melanoma patient, and trametinib and vemurafenib in patients with BRAF V600E mutation). Therefore, it is reasonable to use 10% as the null hypothesis for testing the anti-tumor activity of MK-3475 against putative chemotherapies in this population. With 80 patients treated at a dose level, the study has 93% power to reject the null hypothesis at a type I error rate of 2.5% (one-sided) when the true response rate of MK-3475 is 25%. A p-value of 2.5% approximately corresponds to a 19% empirical response rate when sample size is 80. With the prevalence of high PD-L1 projected to be from 40% to 60%, the number of high PD-L1 patients treated at a dose level ranges from 32 to 48 and the half-width of the 95% confidence intervals for RR at a dose level approximately ranges from 14% to 17% when the empirical RR in the high PD-L1 group is 50% and from 13% to 16% when the empirical RR in the high PD-L1 group is 70% or is 30%. With 32 to 48 patients in the PD-L1 high group, the study has 79% to 94% power to reject the null hypothesis of 10% RR at type I error rate of 2.5% (one-sided) when the true RR is 30%.

Part C NSCLC (single arm)

With 35 NSCLC patients treated at RP2D, the study has approximately 80% power to rule out a ≤9% RR (null hypothesis) when the true RR is 22% at the 10% type I error rate (one-sided).

Part D ipilimumab-naïve *enrolled after Amendment 04 (randomized)*

With 44 patients treated at 2 mg/kg and 44 treated at 10 mg/kg, the study has 80% power to detect 30% vs. 10% or 90% power to detect 25% vs 5% in RR between the two dose levels at the 10% type I error rate (one-sided). A p-value of 10% approximately corresponds to a 12% empirical difference in RR.

With 44 patients treated at a dose level, the study has 89% power to test the null hypothesis of RR=10% at 2.5% type I error rate (one-sided) when the true RR is 30%. A p-value of 2.5% approximately corresponds to an empirical RR of 23% (10/44).

Based on preliminary data from the non-randomized patients, the RR appears similar between the ipi-refractory population and the ipi-naïve population. A pooled analysis of the PD-L1 high patients from Part B (randomized) and Part D (randomized) will be conducted. It is expected that 50-75 PD-L1 high patients will be treated at a dose level in the pooled analysis. With this sample size, the study has >95% power to reject the null hypothesis of 10% RR at type I error rate of 2.5% (one-sided) when the true RR is 30%.

Part B enrolled after Amendment 04 (randomized: 10 mg/kg Q3W vs 10 mg/kg Q2W)

A total of approximately 230 patients will be randomized 1:1 to 10 mg/kg Q3W or 10 mg/kg Q2W, stratified by ipi-naïve vs non ipi-naive. Based on preliminary data from non-randomized patients, the RR appears similar between the non ipi-naive population and the ipi-naïve population. The primary analysis of this cohort is based on a pooled analysis, stratified by ipilimumab treatment history. Subgroup analyses will also be conducted. With 230 patients, the study has ~85% power to detect a 20% difference (i.e., 30% vs 50%) in RR between the two doses at the 2.5% type I error rate (one-sided). A p-value of 2.5% approximately corresponds to a 13% empirical difference in RR.

Similar to randomized cohorts in Part B and Part D between 10 mg/kg Q3W vs 2 mg/kg Q3W, anti-tumor activities of MK-3475 at a dose schedule as well as related to PD-L1 expression will also be investigated.

Part F NSCLC 1L *PD-L1 positive (randomized)*

With 44 patients per dose level, the study has 86% power to detect a 25% difference in RR (i.e., 45% vs 20%) at alpha=10% (1-sided) between two dose levels. A P-value of 10% approximately corresponds to a 13% empirical difference in RR.

With 44 1L patients treated at a dose level, the study has 91% power to test the null hypothesis of RR=25% at 2.5% type I error rate (one-sided) when the true RR is 50%. A p-value of 2.5% approximately corresponds to an empirical RR of 41% (18/44).

Part F NSCLC 3L+ (single arm)

With 32 3L+ patients treated at 10 mg/kg, the study has 90% power to test the null hypothesis of RR=10% at 2.5% type I error rate (one-sided) when the true RR is 35%. A p-value of 2.5% approximately corresponds to an empirical RR of 25% (8/32).

Part F NSCLC 1L PD-L1 negative (single arm)

With 20 patients treated at 10 mg/kg Q2W, the study has 90% power to rule out a >30% RR if <4 patients respond (i.e., probability of observing < 4 responses is 10% when true RR is 30%).

Part F NSCLC 2L+ PD-L1 positive (randomized)

Approximately 250 patients will be randomized (3:2) to 10 mg/kg Q3W and 10 mg/kg Q2W. The randomization may be stratified by PD-L1 expression level based on a preliminary cutoff point once available (see Section 3.5.5.4 for details). With 250 patients, the study has approximately 95% power to detect a 15% difference in RR between the two doses at type I error rate of 10% (one-sided) assuming that the RR at 10 mg/kg Q3W is 10%.

Enrollment of patients with weakly positive tumors will be capped at 50% so that at least 75 patients with strongly positive tumors will be treated at 10 mg/kg Q3W. With 75 patients treated at 10 mg/kg Q3W, the study has 85% power to detect a 15% difference in RR between MK-3475 and historical control which is conservatively estimated to be 15% (i.e., 30% vs 15%) at type I error rate of 2.5% (one-sided). A p-value of 2.5% approximately corresponds to an empirical RR of 25% (i.e., the lower bound of the 95% CI for an empirical RR at 25% will exclude 15%). With 50 patients at 10 mg/kg Q2W, the study has 68% (or 89%) power to detect a 15% (or 20%) difference in RR between MK-3475 and historical control at type I error rate of 2.5% (one-sided). A p-value of 2.5% approximately corresponds to an empirical RR of 28% (i.e., the lower bound of the 95% CI for an empirical RR at 28% will exclude 15%). If 10 mg/kg Q2W has comparable anti-tumor effect to 10 mg/kg Q3W in the population, the two doses will be pooled for a joint analysis as appropriate. Regardless, if the primary analysis in the biomarker strongly positive population is positive a step-down analysis will be performed to assess all biomarker positive patients including patients with weakly positive tumors.

If Part F data show no evidence that line of therapy (1L vs 2L+) impacts efficacy, data will be combined across line of therapy and within dose for more powerful assessment of difference in RR between the two dose schedules and for more precise estimation of RR at a dose schedule. The pooled analysis will be conducted in the overall biomarker positive population as well as in the strongly biomarker position population, as appropriate.

PD-L1 biomarker effect

Kendall's tau statistic will be used for testing the PD-L1 biomarker effect for various tumor and treatment groups. All testing will be conducted at type I error rate of 2.5% (one-sided). For a sample size of *approximately 45* patients with both post-treatment disease assessments and valid evaluation of baseline PD-L1 expression levels in *newly obtained* tumor biopsies, the study has approximately 90% power to detect a one-fold difference in concordance (i.e., odds of concordance relative to discordance = 2, or in other words tumor is twice more likely to reduce than to increase if the patient's tumor

has high expression of the PD-L1 than low expression). When the sample size is reduced to *25* patients, Kendall's tau has 90% power to detect a 1.5 to 2-fold difference in concordance. *In addition, the Youden index and other methods will be used for biomarker cut-off point analysis.*

Section 3.5.9 Interim Analysis

The study will have two planned interim analyses for ipilimumab-naïve patients *treated at 10 mg/kg* in Part B *(non-randomized)*.

Part F *1L* NSCLC *PD-L1 positive Patients*

For each dose level in Part F *1L*, an interim analysis will be conducted after the first 20 patients have had a 3-month follow-up. The accrual to a dose level may be put on hold if ≤2 patients have a response. The probability of observing ≤2 responses out of 20 patients is <10% when the true RR is 25%. After a review of totality of data including tumor volumetric change, disease control rate and safety, the Sponsor will make a decision on whether to resume the accrual.

Part F 2L+ NSCLC PD-L1 positive Patients

There is one planned interim analysis. The primary objective of the interim analysis is to potentially exclude patients with weakly positive tumors (based on final cutoff point) from further enrollment. Based on current projection, the randomized portion may take 11 months to accrue. More interim analyses may be conducted if the accrual rate is slower than expected.

The interim analysis will be conducted after 60 patients in the randomized portion have a minimum follow-up of 12 weeks, which is expected to occur approximately 7 months after the randomization. The final PD-L1 assay cutoff point for efficacy analyses will be determined before this IA will occur. The target response rate is 20% for interim futility decisions. As guidance, if less than 3 out of 30 patients with weakly positive tumors (i.e., <10%) have a confirmed response no further patients with weakly positive tumors (based on final cutoff point) will be enrolled. The probability of observing less than 3 responses is <4% when the true response rate is 20%. When sample sizes are slightly different, an empirical response rate of <10% will be used as a reference or futility decisions which will also take into account the totality of data. Because the two dose schedules may have different cutoff points, a subgroup analysis by dose schedule will be conducted to determine whether to exclude patients with weakly positive tumors for one schedule or for both (see Section 3.5.5.4 for more details).

Additional Interim Analyses

In addition to the above interim analyses, an interim analysis of Part C may be conducted after all patients have had a 3-month follow-up, interim analyses of Part B ipilimumab-refractory patients and Part D ipilimumab-naive patients (timings to be determined) may

be conducted to assist with the dose-selection decision for planning phase 2 studies in melanoma patients, *and interim analyses may also be conducted to determine the cutoff points for high PD-L1 patients in melanoma and NSCLC patients (see Section 3.5.5.4).*

Section 3.6.1 Patient and Replacement Information

MK-3475 clinical supplies will be packaged to support enrollment of approximately *1047* patients

Section 3.6.4 Secondary Packaging and Labeling Information (kit)

Supplies *may* be packaged **in kit boxes containing 1 vial**. Kit configuration is subject to change as a result of packaging constraints.

*If secondary packaging is utilized, l*abel text may include the following: