Official Protocol Title:	Phase I Study of Single Agent Pembrolizumab (MK-3475) in Patients with Progressive Locally Advanced or Metastatic Carcinoma, Melanoma, and Non-Small Cell Lung Carcinoma(KEYNOTE 001)
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SPONSOR:

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TITLE:

Phase I Study of Single Agent Pembrolizumab (MK-3475) in Patients with Progressive Locally Advanced or Metastatic Carcinoma, Melanoma, and Non-Small Cell Lung Carcinoma (KEYNOTE 001)

INVESTIGATOR:

PRIMARY:

CLINICAL PHASE: I

US IND NUMBER: 110,080

SITE:

INSTITUTIONAL REVIEW BOARD/ETHICS REVIEW COMMITTEE:

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SUMMARY OF CHANGES

PRIMARY REASON(S) FOR THIS AMENDMENT:

Section Number(s)	Section Title(s)	Description of Change(s)	Rationale
3.2.5.4.4	Guidelines for Dose Modifications Supportive Care Guidelines	Dose modification and supportive care guidelines were updated.	To add myocarditis grade clarification and provide action for dose modification evaluations.
3.2.5.4.5		Former Section 3.2.5.4.5 was deleted as this information is now provided in Section 3.2.5.4.4	
3.2.5.4.7	Duration of Follow-up	The following sentence was deleted: "Sites may collect survival information with unscheduled calls if needed for additional analyses purposes." A new section, Section 3.2.5.4.8, was added:	To allow flexibility in the entire follow-up period beyond just the current Survival Follow-up portion to enable more frequent follow-ups as necessary. Added in addition to the approximately 12-week follow up that would allow us to perform additional OS assessments should there be a need.
3.2.5.4.8	Survival Follow-up	"Subjects who move into the Survival Follow-up Phase should be contacted by telephone approximately every 90 days ± 28 days to assess for survival status until death,	

Section Number(s)	Section Title(s)	Description of Change(s)	Rationale
		withdrawal of consent, or the end of the trial, whichever occurs first. Refer to the Study Flow Chart (Section 1.7; Parts B, C, D, and F: Follow-up."	
3.2.5.5	Survival Status	A new section, Section 3.2.5.5, was added: To ensure current and complete survival data is available at the time of database locks, updated survival status and its respective entry into the database may be requested during the course of the study by the Sponsor. For example, updated survival status may be requested prior to but not limited to an external Data Monitoring Committee (eDMC) review, interim and/or final analysis. Upon Sponsor notification, all participants who do not/will not have a scheduled study visit or study contact during the sponsor defined time period will be contacted for their survival status (excluding participants	

Section Number(s)	Section Title(s)	Description of Change(s)	Rationale
		that have previously recorded a death event in the collection tool).	

ADDITIONAL CHANGE(S) FOR THIS AMENDMENT:

Section Number(s)	Section Title(s)	Description of Change(s)	Rationale
1.4	Summary of Study Design	The following was added: "After the study has achieved its key objective or the study has ended, the participant is discontinued from the study and will be enrolled in an extension study to continue protocol-defined assessments including subject status updates and treatment."	When a protocol closes, patients will be transitioned to an extension study.
3.2.5.4.5	Duration of Therapy	The following was added: "Upon study completion, participants are discontinued and enrolled in a pembrolizumab extension study."	

Section Number(s)	Section Title(s)	Description of Change(s)	Rationale
1.5	Sample	Current protocol language was updated from: "As of 13 July, 2014, a total of 1260 patients were enrolled in the study; 32 patients in Part A, 564 in Part B, 41 patients in Part C, 104 patients in Part D, 519 patients in Part F)." To: *"A total of* 1260 patients were enrolled in the study; 32 patients in Part A, 564 patients in Part B, 41 patients in Part C, 104 *patients* in Part D, *and* 519 patients in Part F)."	Enrollment is complete.
1.6	Dosage/Dosage Form, Route, and Dose Regimen	The following was added: "Note: patients who discontinued pembrolizumab due to an AE are not eligible for Second Course."	To include clarification that patients who discontinued pembrolizumab due to AEs are not eligible for Second Course treatment.
1.6	Dosage/Dosage Form, Route, and Dose Regimen	Current protocol language was updated from: "These patients are eligible for second course treatment if they experienced an investigator determined confirmed radiographic disease progression according to irRECIST and satisfy the requirements	Confirmation of PD is not required prior to starting Second Course treatment. Investigator assessment must be based on irRC guidelines. irRECIST" does not apply for this protocol.

Section Number(s)	Section Title(s)	Description of Change(s)	Rationale
		mentioned in 3.2.5.4.9." To: "These patients are eligible for Second Course treatment if they experienced an investigator determined radiographic disease progression *and satisfy the requirements mentioned in Section 3.2.5.4.9.*"	
1.7	Study Flow Chart: Part A, B, & D	PK assessments were deleted. The following assessments were updated: CBC with Differential Chemistry Panel Pregnancy Test Thyroid Function Survival Status Imaging Assessments	Consistent results have been seen for PK across multiple indications which justify removing the collection of additional PK. Changes to CBC with differential, chemistry, pregnancy, thyroid status, and imaging assessments were inadvertently omitted with Amendment 10. Changes to survival assessments were made to allow flexibility in the entire follow-up period beyond just the current Survival Follow-up portion to enable more frequent follow-ups as necessary. Please refer to the Amendment 11 Investigator's Imaging Operations Manual (IIOM) for imaging requirements.

Section Number(s)	Section Title(s)	Description of Change(s)	Rationale
1.7	Study Flow Chart: Part C & F	PK assessments were deleted. The following assessments were updated: CBC with Differential Chemistry Panel Pregnancy Test Thyroid Function Survival Status Imaging Assessments	Consistent results have been seen for PK across multiple indications which justify removing the collection of additional PK samples. Changes to CBC with differential, chemistry, pregnancy, thyroid status, and imaging assessments were inadvertently omitted with Amendment 10. Changes to survival assessments were made to allow flexibility in the entire follow-up period beyond just the current Survival Follow-up portion to enable more frequent follow-ups as necessary. Please refer to the Amendment 11 Investigator's Imaging Operations Manual (IIOM) for imaging requirements.
1.7	Study Flow Chart: Part A, B, C, D, F: Follow-up	PK assessments were deleted. Survival status assessments were updated.	Consistent results have been seen for PK across multiple indications which justify removing the collection of additional PK samples. Changes to survival assessments were made to allow flexibility in the entire follow-up period beyond just the current Survival Follow-up portion to enable more frequent follow-ups as necessary.

Section Number(s)	Section Title(s)	Description of Change(s)	Rationale
1.7	Study Flow Chart: Second Course Phase	PK assessments were deleted. The following assessments were updated: CBC with differential Chemistry Panel Pregnancy Test Survival Status Thyroid Function Imaging Assessments	Consistent results have been seen for PK across multiple indications which justify removing the collection of additional PK samples. Changes to CBC with differential, chemistry, pregnancy, thyroid status, and imaging assessments were inadvertently omitted with Amendment 10. Please refer to the Amendment 11 Investigator's Imaging Operations Manual (IIOM) for imaging requirements. Changes to survival assessments were made to allow flexibility in the entire follow-up period beyond just the current Survival Follow-up portion to enable more frequent follow-ups as necessary.

Section Number(s)	Section Title(s)	Description of Change(s)	Rationale
1.7	Study Flow Chart: Second Course Phase: Follow-Up	Footnote 5 was deleted and replaced with: "Imaging should be continued for patients who discontinue from the Second Course Phase for reasons other than PD until PD is determined."	This was inadvertently included Amendment 10. Patients who discontinue from the Second Course Phase for reasons other than PD would go into regular FU and then survival, however; they would continue with scans if they discontinued for other reasons than PD.

Section Number(s)	Section Title(s)	Description of Change(s)	Rationale
2.1.2 2.5 3.2.5.4.1 3.3.2 3.5.3.3 3.5.4.3 3.5.5.2 3.5.5.3 3.5.5.5	Secondary Objectives List of Efficacy/Pharmacokinetic/Immunogenicity Measurements Study Visits Pharmacokinetic Measurements PK and PD Endpoints PK and PD Analyses Pharmacokinetic Analysis Pharmacodynamic Analysis Safety Analysis	These sections were updated to clarify that as of Amendment 11, samples are no longer being collected for PK analysis.	Consistent results have been seen for PK across multiple indications which justify removing the collection of additional PK samples.
3.1.3	Rationale for Dose	The most up-to-date dose justification language submitted to FDA was added	For clarification and consistency.
2.4.1 3.3.1.3	Summary of Study Design Radiographic Assessments	Imaging assessments were updated	Please refer to the Amendment 11 Investigator's Imaging Operations Manual (IIOM) for imaging requirements.

Section Number(s)	Section Title(s)	Description of Change(s)	Rationale
3.2.4.3	Use in Pregnancy	Current standard pembrolizumab (MK-3475) text was added.	For clarification and consistency with new standard Merck protocol text for pembrolizumab (MK-3475).
3.2.5.4.4.1 (formerly 3.2.5.4.5.1)	Adverse Events of Special Interest: Immune Related Adverse Events	Table 3-4 was deleted. The following was updated from: "Selected non-serious adverse events listed in Table 3-4 should be entered in the database if they are considered drug related." To: Selected *irAEs are defined as Adverse Events of Special Interest (AEOSI) and must be reported to the Sponsor. A list of AEOSI are provided in the Pembrolizumab AEOSI Preferred Term List document. AEOSIs* should be entered in the database if they are considered drug related."	Table 3-4 will be placed in a separate document that will be released with the protocol. To clarify that irAEs are defined as AEOSIs.
2.5	List of Efficacy/Pharmacokinetic /Immunogenicity Measurements	The following note was added: "Note: As of Amendment 10, anti-pembrolizumab (MK-3475) antibodies are no longer being collected"	As of Amendment 10 anti-pembrolizumab antibodies are no longer being collected. This language was removed from all applicable sections of the protocol but was inadvertently left in this section with the last amendment.

Section Number(s)	Section Title(s)	Description of Change(s)	Rationale
3.2.5.4.5	Duration of Therapy	Current protocol language was updated from: Patients who have a confirmed complete response by two scans ≥4 weeks apart and who have been on pembrolizumab (MK-3475) treatment for at least 6 months may discontinue pembrolizumab (MK-3475) treatment at the discretion of the investigator *after receiving at least two doses beyond the initial determination of CR*. To: Patients who have a confirmed complete response by two scans ≥4 weeks apart and who have been on pembrolizumab (MK-3475) treatment for at least 6 months may discontinue pembrolizumab (MK-3475) treatment at the discretion of the investigator.	Two additional doses beyond initial determination of CR are no longer required. This language was removed from all applicable sections of the protocol but was inadvertently left in this section with the last amendment.
3.2.5.4.6	Safety Follow-up Visit	Current protocol language was updated from: 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.	To clarify that the mandatory safety follow-up visit should also be conducted before initiation of a new anticancer treatment if this occurs earlier than 30 days after the last dose of trial treatment.

Section Number(s)	Section Title(s)	Description of Change(s)	Rationale
		To: The mandatory Safety Follow-up Visit should be conducted approximately 30 days after the last dose of trial treatment or before the initiation of a new anticancer treatment, whichever comes first.	
3.2.5.4.6	Safety Follow-up Visit	Current protocol language was updated from: "The patient will be monitored for all adverse events up to the mandatory 30 day Safety Follow-Up Visit and SAEs through the FU1 visit (90 days) 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."	For clarification and consistency with new standard Merck protocol text for pembrolizumab (MK-3475).

Section Number(s)	Section Title(s)	Description of Change(s)	Rationale
		To: "All AEs that occur prior to the Safety Follow-Up Visit should be recorded. Subjects with an AE of Grade >1 will be followed until the resolution of the AE to Grade 0 to 1 or until the beginning of a new anticancer therapy, whichever occurs first. Serious AEs that occur within 90 days of the end of treatment or before initiation of a new anticancer treatment should also be followed and recorded."	
3.2.5.7	Discontinuation/Withdrawal From the Study	Current standard pembrolizumab (MK-3475) text was added.	For clarification and consistency with new standard Merck protocol text for pembrolizumab (MK-3475).
3.4.2	Recording Adverse Experiences	The following was updated from: "With amendment 10, investigators are required to report SAEs and drug related NSAEs if they meet criteria for AEOSI in Table 3-4 or are ECIs described in section 3.4.8 below. Previous ECI guidance is now updated in amendment 10 and is no longer required to be reported to Merck safety group. We do require InForm entry of select DRUG-RELATED NSAEs listed in Table 3-4. Other NSAEs do not need to be reported."	To update and clarify AEOSI reporting procedure.

Section Number(s)	Section Title(s)	Description of Change(s)	Rationale
		"From the time of treatment allocation/randomization through 30 days following cessation of treatment, all serious adverse events and drug related adverse events of special interest must be reported by the investigator. Such events will be recorded at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in section 3.4.5.1." To: "With Amendment 10, investigators are required to report SAEs and drug related NSAEs if they meet criteria for AEOSI *(refer to the Pembrolizumab AEOSI Preferred Term List document)* or are ECIs described in Section 3.4.8 *below. Previous* ECI guidance is now updated in Amendment10 and is no longer required to be reported to Merck safety *group. Other* NSAEs do not need to be reported."	

Section Number(s)	Section Title(s)	Description of Change(s)	Rationale
4.5	Compliance with Information Program on Clinical Trials for Serious or Life Threatening conditions	Current standard pembrolizumab (MK-3475) text was added.	For clarification and consistency with new standard Merck protocol text for pembrolizumab (MK-3475).

1. SUMMARY

1.1 TITLE

Phase I Study of Single Agent Pembrolizumab (MK-3475) in Patients with Progressive Locally Advanced or Metastatic Carcinoma, Melanoma, and Non-Small Cell Lung Carcinoma. (KEYNOTE 001)

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

The programmed cell death 1 (PD-1) pathway represents a major immune control switch which may be engaged by tumor cells to overcome active T-cell immune surveillance [1]. The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in various tumors [2-5]. High expression of PD-L1 on tumor cells (and to a lesser extent of PD-L2) has been found to correlate with poor prognosis and survival in various cancer types, including renal cell carcinoma (RCC) [6], pancreatic carcinoma [7], hepatocellular carcinoma [8], ovarian carcinoma [9] and NSCLC [77]. Furthermore, PD-1 has been suggested to regulate tumor-specific T-cell expansion in patients with malignant MEL [10].

Preclinical in vitro and in vivo experiments have shown that PD-1 and/or PD-L1 blockade using monoclonal antibodies (mAb) enhances tumor-cell specific T-cell activation, cytokine production, anti-tumor effector mechanisms, and clearance of tumor cells by the immune system [8; 12; 13; 14; 15; 16]. Recent data of Nivolumab (BMS-936558, MDX-1106), an IgG4 antibody against PD-1, have validated PD-1 as an attractive target for clinical therapeutic intervention [17]. Nivolumab was tested in multiple solid tumors and promising clinical activity was noted in MEL, RCC, and non-small cell lung carcinoma (NSCLC). The most common adverse events (AEs) were immune-related (also referred to as AEs of special interest), with an overall incidence of approximately 20% [17]. Most commonly observed were pruritus, skin rash, and diarrhea. Other immune-related AEs (irAEs) include increase of TSH, increase of ALT/AST, pneumonitis, infusion reaction and vitiligo [18].

Pembrolizumab (MK-3475) (previously known as SCH 900475) is a potent and highly selective humanized mAb of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Pembrolizumab (MK-3475) strongly enhances T lymphocyte immune responses in cultured blood cells from healthy human donors, cancer patients, and primates. In T cell activation assays using human donor blood cells, the EC50 was in the range of 0.1 to 0.3 nM. Pembrolizumab (MK-3475) also modulates the level of interleukin-2 (IL-2), tumor necrosis factor alpha (TNFα), interferon gamma (IFNγ), and other cytokines. The antibody potentiates existing immune responses only in the presence of antigen and does not nonspecifically activate T cells (for details see the pembrolizumab [MK-3475] Investigator's Brochure).

The present study has 5 parts. The main objectives of Part A are to evaluate safety and tolerability, PK and pharmacodynamics, to determine a maximum tolerated dose (MTD) up to 10 mg/kg and preliminary recommended phase 2 doses (RP2D). The main objectives of Part B are to characterize the safety profile and tolerability of pembrolizumab (MK-3475) at the RP2D(s), to evaluate the clinical activity of pembrolizumab (MK-3475) in patients with MEL and to investigate the correlation of biomarkers such as PD-L1 and anti-tumor activity of pembrolizumab (MK-3475). The main objectives of Part C are to characterize the safety profile and tolerability of pembrolizumab (MK-3475) at the preliminary RP2D(s), to evaluate the clinical activity of pembrolizumab (MK-3475) in patients with NSCLC and to investigate the correlation of biomarkers such as PD-L1 and anti-tumor activity of pembrolizumab (MK-3475). The main objectives of Part D are to characterize the safety profile and tolerability of pembrolizumab (MK-3475) and to evaluate the clinical activity of pembrolizumab (MK-3475) in patients with ipilimumab-naïve MEL at 2 mg/kg and 10 mg/kg. The main objectives of Part F are to characterize the safety profile and tolerability of pembrolizumab (MK-3475) in patients with NSCLC and to evaluate the clinical activity of pembrolizumab (MK-3475) monotherapy in a first-line setting at 10 mg/kg every 2 weeks (Q2W) and every 3 weeks (Q3W) and second-line or greater settings at 2 mg/kg and 10 mg/kg Q2W and Q3W, in a mostly PD-L1 enriched population, and to investigate the extent of tumor response that correlates with the degree of biomarker positivity in patients treated with monotherapy. The Investigator's Brochure (IB) for pembrolizumab

(MK-3475) provides comprehensive background information on the mechanism of action of the mAb and the non-clinical data, including PK, pharmacodynamics, safety profile and anti-tumor activity.

1.4 SUMMARY OF STUDY DESIGN

This is an open-label, Phase I study of intravenous (IV) pembrolizumab (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 pembrolizumab (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 pembrolizumab (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. In **Part F-3**, NSCLC patients with prior systemic therapy whose tumors express PD-L1 will be enrolled at 2 mg/kg Q3W to better characterize the efficacy and safety profile of pembrolizumab (MK-3475) monotherapy and for 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 pembrolizumab (MK-3475).

With Amendment 10, all remaining and ongoing subjects will be treated with fixed dosed 200 mg every 3 weeks (not weight based). The rationale for fixed dose regimen is outlined below.

After the study has achieved its key objective or the study has ended, the participant is discontinued from this study and will be enrolled in an extension study to continue protocol-defined assessments including subject status updates and treatment.

1.5 SAMPLE

A total of approximately 1137 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 480 patients in Part F. (A total of 1260 patients were enrolled in the study; 32 patients in Part A, 564 patients in Part B, 41 patients in Part C, 104 patients in Part D, and 519 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 ipilimumab-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 480 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 pembrolizumab (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 pembrolizumab (MK-3475) at 10 mg/kg Q3W. Under Amendment 07 and beyond, 280 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 pembrolizumab (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 pembrolizumab (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.

F-3 will be added under Amendment 09 and will enroll an additional 40 previously-treated NSCLC patients with at least one prior line of systemic treatment whose tumors express PD-L1. All patients in F-3 will be assigned manually by the Sponsor and will be treated with pembrolizumab (MK-3475) at 2 mg/kg every 3 weeks. 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, F-2, and F-3 cohorts will occur concurrently.

1.6 DOSAGE/DOSAGE FORM, ROUTE, AND DOSE REGIMEN

All subjects will receive fixed dose of 200 mg every 3 weeks (Q3W) under Amendment 10. The rationale for fixed dose 200 mg every 3 weeks is outlined in Section 3.1.3.

Pembrolizumab (MK-3475) will be administered as a 30 minute IV infusion, with a window of -5 and +10 minutes. 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 pembrolizumab (MK-3475) treatment for at least 6 months may discontinue pembrolizumab (MK-3475) treatment at the discretion of the investigator. Pembrolizumab (MK-3475) may be resumed (Second Course treatment) upon disease recurrence in these patients. Note: patients who discontinued pembrolizumab due to an AE are not eligible for Second Course. See Section 3.2.5.4.8 for details regarding follow up for CR patients who discontinue treatment with pembrolizumab (MK-3475), and

Section 3.2.5.4.9 for details regarding eligibility for second course treatment and Section 1.7 (Study Flow Chart) for details on procedures.

With Amendment 10, patients who have SD or PR may discontinue study treatment as long as they completed at least 24 months of treatment with pembrolizumab (MK-3475) and did not discontinue pembrolizumab (MK-3475) due to AEs. These patients are eligible for Second Course treatment if they experienced an investigator determined radiographic disease progression and satisfy the requirements mentioned in Section 3.2.5.4.9.

1.7 STUDY FLOW CHART

Part A, B, & D: 3 Week Schedule

	Screening (-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															
Vital Signs/Weight [1]	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
Review Adverse Events [2]		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 [3]	X	←	—	—	—	—	—	—	—	—	—	—	—	—	→
Chemistry Panel[4]	X	←	—	—	—	—	—	—	—	—	—	—	—	—	→
Pregnancy Test - Urine or Serum β-HCG [5]		←	—	—	—	—	—	—	—	—	—	—	—	—	→
Thyroid Function [6]		X	X		X		X		X		X		X		X
Survival Status [7]		←	- -	- -	- -	- -	- -	- -	- -	- -	- -	- -	- -	- -	→
Efficacy Measurements															
Tumor Imaging [8]	X					X				X				X	X
Drug Administration															
Study Drug Administration (30 minute infusion)		X	X	X	X	X	X	X	X	X	X	X	X	X	X

1. Vital signs to include temperature, pulse, respiratory rate and blood pressure.
2. 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.
3. CBC will be done per standard of care.
4. Chemistry panel will be tested per standard of care.
5. For women of reproductive potential, monthly pregnancy testing should be conducted as per local regulations where applicable. 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.
6. Analysis of T3 or FT4 and TSH will be performed by a central laboratory at cycle 1, 2, and every other cycle thereafter.
7. Updated survival status and its respective entry into the database may be requested by the Sponsor at any time during the course of the study. Upon Sponsor notification, all participants who do not/will not have a scheduled study visit or study contact during the Sponsor defined time period will be contacted for their survival status (excluding participants that have a death event previously recorded), (see Section 3.2.5.5).
8. Tumor imaging will be performed approximately every 16 weeks (112 days) (±28 days) from the first dose of study medication through Year 3, and then Q6 months (24 weeks) (+/- 28 days) through Years 4 and 5. After 5 years, imaging will be performed annually or per institutional standard of care. Response status will be assessed by the study site. Refer to Section 3.3.1.3 of the protocol for additional information. The same imaging technique must be used in a patient throughout the study. After first documentation of response or progression, repeat imaging will be required approximately 4 weeks later for confirmation, as per immune related response criteria (irRC) guidelines (see Appendix 6.5), (see Section 2.4.1).

Part C and F: 3 Week Schedule

	Screening (-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															
Vital Signs/Weight [1]	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
Review Adverse Events [2]		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 [3]	X	⟷													
Chemistry Panel [4]	X	⟷													
Survival Status		⟷													
Study Procedures															
Pregnancy Test - Urine or Serum β-HCG		X[5]													X
Thyroid Function[6]		X	X		X		X		X		X		X		X
Efficacy Measurements															
Tumor Imaging [8]	X				X			X			X			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															

1. Vital signs to include temperature, pulse, respiratory rate and blood pressure.
2. 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.
3. CBC will be done per standard of care.
4. Chemistry panel will be tested per standard of care.
5. For women of reproductive potential, monthly pregnancy testing should be conducted as per local regulations where applicable. 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.
6. Analysis of T3 or FT4 and TSH will be performed by a central laboratory at cycle 1, 2, and every other cycle thereafter.
7. Updated survival status and its respective entry into the database may be requested by the Sponsor at any time during the course of the study. Upon Sponsor notification, all participants who do not/will not have a scheduled study visit or study contact during the Sponsor defined time period will be contacted for their survival status (excluding participants that have a death event previously recorded), (see Section 3.2.5.5).
8. Tumor imaging will be performed approximately every 9 weeks (63 days) (±28 days) from the first dose of study medication through Year 2, then Q16 weeks (112 days) (±28 days) through Year 3, and Q6 months (24 weeks) (±28 days) through Years 4 and 5. After 5 years, imaging will be performed annually or per institutional standard of care. Response status will be assessed by the study site. 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. The same imaging technique must be used in a patient throughout the study. After first documentation of response or progression, repeat imaging will be required approximately 4 weeks later for confirmation, as per immune related response criteria (irRC) guidelines (see Appendix 6.5), (see Section 2.4.1).

Part A, 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
Approx Months from Last Dose	*1*	*3*	*6*	*Q 90 days after FU 2*
Visit		FU 1	FU 2 [4]	SFU N
Vital Signs/Weight [5]	X	X	X	
Review Adverse Events [6]	X	X	X	
Review Medications	X			
Thyroid Function [6]	X			
CBC with Differential	X			
Comprehensive Serum Chemistry Panel [7]	X			
Tumor Imaging [8]	X	X	X	X
Survival [3]	<--------------------------------	--------------------------------	--------------------------------	-------------------------------->

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 ± 28 days. 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 pembrolizumab (MK-3475), or (2) the start of a new cancer therapy, whichever occurs first.
3. Updated survival status and its respective entry into the database may be requested by the Sponsor at any time during the course of the study. Upon Sponsor notification, all participants who do not/will not have a scheduled study visit or study contact during the Sponsor defined time period will be contacted for their survival status (excluding participants that have a death event previously recorded) (see Section 3.2.5.5).
4. Patients who discontinued treatment due to complete response (CR), stable disease (SD), or partial response (PR) 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 pembrolizumab (MK-3475) per the investigator's discretion. Refer to section 3.2.5.4.8
5. Vital signs to include temperature, pulse, respiratory rate and blood pressure.
6. Collection of all AEs through the 30 day Safety Follow up Visit and SAEs through the FU1 visit (90 days). 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. Drug-related AEs should be reported at any time.
7. Analysis of T3 or FT4 and TSH will be performed by a central laboratory.

8. See appendix 6.1 for a list of laboratory tests.
9. 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.

Second Course Phase (Every 3 weeks)

	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
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]	←	—	—	—	—	—	—	—	—	—	—	—	—	→
Chemistry Panel [5]	←	—	—	—	—	—	—	—	—	—	—	—	—	→
Pregnancy Test – Urine or Serum β-HCG [6]	←	—	—	—	—	—	—	—	—	—	—	—	—	→
Thyroid Function [7]	X	X		X		X		X		X		X		X
Tumor Biopsy	X[8]													X
Survival Status [9]	←	- -	- -	- -	- -	- -	- -	- -	- -	- -	- -	- -	- -	→
Efficacy Measurements														
Tumor Imaging [10]	←	—	—	—	—	—	—	—	—	—	—	—	→	X [11]
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 SD, PR, or CR and discontinue treatment may restart trial treatment if they meet the criteria specified in Section 3.2.5.4.9.
2. Vital signs to include temperature, pulse, respiratory rate and blood pressure.
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.
4. CBC will be done per standard of care.
5. Chemistry should be completed per standard of care.
6. For women of reproductive potential, monthly pregnancy testing should be conducted as per local regulations where applicable. 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 or FT4 and TSH will be performed by a central laboratory at cycle 1, 2, and every other cycle thereafter.
8. Patients are encouraged to get a biopsy at progression before receiving pembrolizumab.
9 Updated survival status and its respective entry into the database may be requested by the Sponsor at any time during the course of the study. Upon Sponsor notification, all participants who do not/will not have a scheduled study visit or study contact during the Sponsor defined time period will be contacted for their survival status (excluding participants that have a death event previously recorded), (see Section 3.2.5.5).
10. Tumor imaging (either CT or MRI, with strong preference for CT; lung x-ray) will be performed within 28 days prior to re-starting with pembrolizumab (MK-3475) after relapse from SD, PR or 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.
11. Tumor imaging will be performed Q12 weeks (±28 days) through Year 2 from re-treatment, then Q16 weeks (±28 days) through Year 3, and Q6 months through Years 4 and 5. After 5 years, imaging will be performed annually or per institutional standard of care.

Second Course Phase: Follow-Up

	Safety Follow-up Visit 30 Days (± 3) From Last Dose [1]	Follow-Up (FU) [2]		Long Term Follow-up [3]
Approx Months from Last Dose	*1*	*3*	*6*	*Q 90 days after FU 2*
Visit		FU 1	FU 2[5]	SFU N
Vital Signs/Weight [6]	X	X	X	
Review Adverse Events [7]	X	X	X	
Review Medications	X			
Thyroid Function [8]	X			
CBC with Differential	X			
Chemistry Panel	X			
Tumor Imaging [9]	X	X	X	X
Survival [4]	←--------------------------------	--------------------------------	--------------------------------	--------------------------------→

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 ± 28 days. 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 pembrolizumab (MK-3475), or (2) the start of a new cancer therapy, whichever occurs first.
3. Each Survival Follow-Up Visit (SFU) has a visit window of ± 28 days, and will be conducted via a phone call. Sites may collect survival information with unscheduled calls if needed for additional analyses purposes. 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 90 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.
4. Updated survival status and its respective entry into the database may be requested by the Sponsor at any time during the course of the study. Upon Sponsor notification, all participants who do not/will not have a scheduled study visit or study contact during the Sponsor defined time period will be contacted for their survival status (excluding participants that have a death event previously recorded) (see Section 3.2.5.5).
5. Imaging should be continued for patients who discontinue from the Second Course Phase for reasons other than PD until PD is determined.
6. Vital signs to include temperature, pulse, respiratory rate and blood pressure.
7. Collection of all AEs through the 30 day Safety Follow up Visit and SAEs through the FU1 visit (90 days). 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. Drug-related AEs should be reported at any time.

8. Analysis of T3 or FT4 and TSH will be performed by a central laboratory at cycle 1, 2, and every other cycle thereafter.
9. 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.

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 pembrolizumab (MK-3475) in adult patients with unresectable advanced carcinoma (including NSCLC or MEL).

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

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

   Hypothesis: Single agent pembrolizumab (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 pembrolizumab (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 pembrolizumab (MK-3475) in unselected MEL refractory to ipilimumab patients and MEL patients refractory to ipilimumab with PD-L1 expressing tumors.

   Hypothesis: Single agent pembrolizumab (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 pembrolizumab (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 pembrolizumab (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 pembrolizumab (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 pembrolizumab (MK-3475).

   Note: As of Amendment 11, PK samples are no longer being collected (see Section 3.3.2).

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 pembrolizumab (MK-3475):

   - To evaluate the correlation between PD-L1 expression levels and anti-tumor activity of pembrolizumab (MK-3475) in patients with melanoma, excluding ipilimumab-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 pembrolizumab (MK-3475) versus baseline.

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

6) To evaluate response duration, progression-free survival and overall survival of NSCLC patients who are treated with pembrolizumab (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 beyond, 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 and F-3 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 or F-3 is found to have one molecular alteration (either sensitizing EGFR mutation or ALK translocation), then testing for the other alteration is not required.

    - For patients in F-1, F-2, or F-3, if a patient is known to have a mutation in KRAS, then testing for an EGFR mutation or for an ALK translocation will not be required given that all of these molecular alterations are mutually exclusive in patients with non-squamous NSCLC.

  - For patients enrolled in F-1, F-2, or F-3, who are known to have a tumor of predominantly squamous histology, molecular testing for EGFR mutation and ALK translocation will not be required as this is not standard of care and is not part of current diagnostic guidelines.

- Randomized patients in F-1, F-2, and F-3 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 beyond, patients in F-2 and F-3 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.
- For F-2 and F-3 cohorts, 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-pembrolizumab (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 from the date of completion of the thoracic radiation before the first dose of pembrolizumab (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 pembrolizumab (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 if the slice thickness is greater than 5 mm. 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.

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 × upper limit of normal (ULN)
Hepatic	
Serum total bilirubin	≤1.5 × ULN **OR**
	Direct bilirubin ≤ULN for patients with total bilirubin levels >1.5 ULN
AST (SGOT) and ALT (SGPT)	≤2.5 × ULN **OR** ≤5 × ULN for patients with liver metastases
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT)	≤1.5 × ULN (Only if not using anticoagulants[2])
Activated Partial Thromboplastin Time (aPTT)	≤1.5 × 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 pembrolizumab (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 pembrolizumab (MK-3475). Note: This does not include participation in the follow-up phase of a study.

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 20 mg hydrocortisone (or 5 mg of prednisone) in the morning and 10 mg hydrocortisone (or 2.5 mg 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 pembrolizumab (MK-3475).

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

9) Patient has a history of non-infectious pneumonitis that has required a course of oral or intravenous steroids to assist with recovery, 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 inhaled steroids or local steroid injections would not be excluded from the study. Patients with hypothyroidism not from autoimmune disease 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 pembrolizumab (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-pembrolizumab (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 3.2.5.4.8 (Duration of Follow-up).

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

With Amendment 10 tumor imaging will be performed approximately every 16 weeks (112 days) (±28 days) from the first dose of study medication through Year 3, and then Q6 months (24 weeks) (±28 days) through Years 4 and 5. After 5 years, imaging will be performed annually or per institutional standard of care. Response status will be assessed by the study site. Refer to Section 3.3.1.3 of the protocol for additional information. The same imaging technique must be used in a patient throughout the study. After first documentation of response or progression, repeat imaging will be required approximately 4 weeks later for confirmation, as per immune related response criteria (irRC) guidelines (see Appendix 6.5), (see Section 2.4.1).

Part B

Part B will only enroll patients with MEL. Pembrolizumab (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 02 will be repeated Q2W. These patients will continue Q2W dosing until they discontinue study therapy. For patients consented under Amendments 03, 04, 05, 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. 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 to 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 pembrolizumab (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. Note: If repeat imaging shows a reduction in the tumor burden compared to the Week 12 scan demonstrating PD, then treatment with pembrolizumab (MK-3475) may continue after Sponsor approval.

The same paradigm for confirmatory scans of response (4 weeks after the initial finding) or progression of disease (4 to 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-pembrolizumab (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 3.2.5.4.8 (Duration of Follow-up).

With Amendment 10 tumor imaging will be performed approximately every 16 weeks (112 days) (±28 days) from the first dose of study medication through Year 3, and then Q6 months (24 weeks) (+/- 28 days) through Years 4 and 5. After 5 years, imaging will be performed annually or per institutional standard of care. Response status will be assessed by the study site. Refer to Section 3.3.1.3 of the protocol for additional information. The same imaging technique must be used in a patient throughout the study. After first documentation of response or progression, repeat imaging will be required approximately 4 weeks later for confirmation, as per immune related response criteria (irRC) guidelines (see Appendix 6.5), (see Section 2.4.1).

Part C

Part C will only enroll patients with NSCLC who have experienced progression after two prior systemic anti-tumor regimens. Pembrolizumab (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-pembrolizumab (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 to 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 pembrolizumab (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. Note: If repeat imaging shows a reduction in the tumor burden compared to the Week 9 scan demonstrating PD, then treatment with pembrolizumab (MK-3475) may continue after Sponsor approval.

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

Tumor imaging will be performed approximately every 9 weeks (63 days) (±28 days) from the first dose of study medication through Year 2, then Q16 weeks (112 days) (±28 days) through Year 3, and Q6 months (24 weeks) (±28 days) through Years 4 and 5. After 5 years, imaging will be performed annually or per institutional standard of care. Response status will be assessed by the study site. 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. The same imaging technique must be used in a patient throughout the study. After first documentation of response or progression, repeat imaging will be required approximately 4 weeks later for confirmation, as per immune related response criteria (irRC) guidelines (see Appendix 6.5), (see Section 2.4.1).

Part D

Part D will only enroll patients with MEL. Pembrolizumab (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.

With Amendment 10 tumor imaging will be performed approximately every 16 weeks (112 days) (±28 days) from the first dose of study medication through Year 3, and then Q6 months (24 weeks) (+/- 28 days) through Years 4 and 5. After 5 years, imaging will be performed annually or per institutional standard of care. Response status will be assessed by the study site. Refer to Section 3.3.1.3 of the protocol for additional information. The same imaging technique must be used in a patient throughout the study.

After first documentation of response or progression, repeat imaging will be required approximately 4 weeks later for confirmation, as per immune related response criteria (irRC) guidelines (see Appendix 6.5), (see Section 2.4.1). Refer to Part A, B, D flowchart in Section 1.7.

Part F

Part F will enroll approximately 480 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 pembrolizumab (MK-3475) at 10 mg/kg Q3W. Under Amendment 07 and beyond, in F-2, an additional 280 patients with 1 or more prior systemic treatments will be treated, 168 at 10 mg/kg Q3W and 112 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 patient 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. Under Amendment 09, an additional 40 patients with one or more prior systemic treatments whose tumors express PD-L1 will be enrolled at 2 mg/kg Q3W. 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.

Tumor imaging will be performed approximately every 9 weeks (63 days) (±28 days) from the first dose of study medication through Year 2, then Q16 weeks (112 days) (±28 days) through Year 3, and Q6 months (24 weeks) (±28 days) through Years 4 and 5. After 5 years, imaging will be performed annually or per institutional standard of care. Response status will be assessed by the study site. 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. The same imaging technique must be used in a patient throughout the study. After first documentation of response or progression, repeat imaging will be required approximately 4 weeks later for confirmation, as per immune related response criteria (irRC) guidelines (see Appendix 6.5), (see Section 2.4.1). Refer to Parts C and F flowchart in Section 1.7.

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°C (101°F) or a sustained temperature of ≥38°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°C (101°F) or a sustained temperature of ≥38°C (100.4°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 pembrolizumab (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 pembrolizumab (MK-3475) as described in Section 3.2.5.4.4 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 001-07/08/09	Total N
Part A Dose Escalation	N=10 [1]					30 Solid Tumor
Part A-1	N=7[1]					
Part A-2		N=13 (Q3W)				
Part B (MEL)	**Ipilimumab naïve** at 10 mg/kg (Q2W)[2] N=41	**Ipilimumab naïve** at 10 mg/kg (Q3W) N=17				58
	Ipilimumab treated at 10 mg/kg (Q2W)[2] N=16	**Ipilimumab treated** at 10 mg/kg (Q3W) N=26				42
		Ipilimumab naïve at 2 mg/kg (Q3W) N=22				22
			Ipilimumab refractory at 10 mg/kg (Q3W) N= 25	**Ipilimumab refractory** at 10 mg/kg (Q3W) N=58		83
			Ipilimumab refractory at 2 mg/kg (Q3W) N= 49	**Ipilimumab refractory** at 2 mg/kg (Q3W) N=41		90
					Ipilimumab naïve, or treated at 10 mg/kg Q2W or Q3W N=147	147

Patient Distribution (cont)

	Amendment 001-02	Amendment 001-03/04	Amendment 001-05	Amendment 001-06	Amendment 001-07/08/09	Total N
Part C (NSCLC)		10 mg/kg (Q3W) N=41				41
Part D (MEL)			**Ipilimumab naïve** at 2 mg/kg (Q3W) N=51			51
			Ipilimumab naïve at 10 mg/kg (Q3W) N=52			52
Part F-1 (NSCLC)				1L: 2 mg/kg (Q3W) N= 6	1L: 10 mg/kg (Q2W) N=47	53[3]
				1L: 10 mg/kg (Q3W) N= 5	1L: 10 mg/kg (Q3W) N= 45	50[3]
Part F-2 (NSCLC)				3L+: 10 mg/kg (Q3W) N=33		33[3]
					3L+: 10 mg/kg (Q2W) N=156	156[4]
					2L+: 10 mg/kg (Q3W) N=172	172[3]
					2L+: 10 mg/kg (Q2W) N=112	112[3]
Part F-3 (NSCLC)					2L+: 2 mg/kg (Q3W) N=55	55[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 3.2.5.4.4.

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-pembrolizumab (MK-3475) antibodies

  Note: As of Amendment 10, anti-pembrolizumab (MK-3475) antibodies are no longer being collected.
- 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.

  Note: As of Amendment 11, PK samples are no longer being collected (see Section 3.3.2).
- 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
- Laboratory tests: complete blood count (CBC), serum chemistry, pregnancy test (at screening and during study when clinically indicated)
- Thyroid function

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; 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 pembrolizumab (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

pembrolizumab (MK-3475) in Cycle 1 and completed all safety evaluations up to and including at least 28 days after the first administration of pembrolizumab (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

3.1.1 Background

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades [1]. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies [21-58]. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells / FoxP3+ regulatory T-cells seems to correlate with improved prognosis and long-term survival in solid malignancies such as ovarian, colorectal and pancreatic cancer, hepatocellular carcinoma, malignant MEL and RCC. TILs can be expanded *ex vivo* and re-infused, inducing durable objective tumor responses in cancers such as MEL [59, 60].

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an Ig superfamily member related to CD28 and CTLA-4 which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) [61, 62]. The structure of murine PD-1 has been resolved [63]. PD-1 and family members are type I transmembrane glycoproteins containing an Ig Variable-type (V-type) domain responsible for ligand binding and a cytoplasmic tail which is responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM). Following T cell stimulation, PD-1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3ζ, PKCθ and ZAP70 which are involved in the CD3 T cell signaling cascade [62, 64-66]. The mechanism by which PD-1 down modulates T cell responses is similar to, but distinct from that of CTLA-4 as both molecules regulate an overlapping set of signaling proteins [5, 67]. PD-1 was shown to be expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B cells, T regs and Natural Killer cells [68, 69]. Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells [70]. The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types, including non-hematopoietic tissues as well as in various tumors [2-5]. Both ligands are type I transmembrane receptors containing both IgV- and IgC-like domains in the extracellular region and contain short cytoplasmic regions with no known signaling motifs. Binding of either PD-1 ligand to PD-1 inhibits T cell activation triggered through the T cell receptor. PD-L1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments. PD-L2 is thought to control immune T cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T cell function in

peripheral tissues [5]. Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T cell inhibitor. High expression of PD-L1 on tumor cells (and to a lesser extent of PD-L2) has been found to correlate with poor prognosis and survival in various cancer types, including RCC [6], pancreatic carcinoma [7], hepatocellular carcinoma [8], and ovarian carcinoma [9]. Furthermore, PD-1 has been suggested to regulate tumor-specific T cell expansion in patients with MEL [10].

The observed correlation of clinical prognosis with PD-L expression in multiple cancers suggests that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention.

Therapeutic studies in mouse models have shown that administration of antibodies blocking PD-1/PD-L1 interaction enhances infiltration of tumor-specific CD8+ T-cells and leads ultimately to tumor rejection, either as a mono-therapy or in combination with other treatment modalities. Anti-mouse PD-1 or anti-mouse PD-L1 antibodies have demonstrated anti-tumor responses as a mono-therapy in models of squamous cell carcinoma, pancreatic carcinoma, MEL and colorectal carcinoma. Blockade of the PD-1 pathway effectively promoted CD8+ T cell infiltration into the tumor and the presence of IFN-γ, granzyme B and perforin, indicating that the mechanism of action involved local infiltration and activation of effector T cell function in vivo [7, 11-15]. In addition, the combination of gemcitabine and anti-PD-L1 mAb demonstrated synergy in the rejection of pancreatic mouse tumors [7]. In-house experiments have confirmed the *in vivo* efficacy of PD-1 blockade as a mono-therapy as well as in combination with chemotherapy in syngeneic mouse tumor models (see the IB).

3.1.2 Rationale for This Study

Recent data of nivolumab, a human IgG4 antibody against PD-1, have validated PD-1 as an attractive target for clinical therapeutic intervention [16]. The repeat dose Phase I study reported a response rate of approximately 30% in patients with advanced MEL and RCC who had failed prior therapy. The same study and an earlier Phase I study of nivolumab [17] also observed anecdotal objective responses in other cancers, such as colorectal carcinoma and non-small cell lung cancer. Of note, all responses were of long duration. The first-in-human study of nivolumab tested 0.3, 1, 3 and 10 mg/kg [17]. The following extended Phase I study tested 1, 3 and 10 mg/kg [16]. There was a relationship between dose and PK [17], but no apparent dose relationship with receptor occupancy in circulating CD3+ cells [17], safety or anti-tumor activity [16, 17]. Nivolumab has generally been well tolerated, however, three drug-related deaths have been reported because of pneumonitis [16, 17]. In the first-in-human study, no DLT was observed [17]. The most common adverse events (AE) of CTCAE Grade ≥2 were decreased CD4+ lymphocyte counts (35.9%), lymphopenia (25.6%), and fatigue and musculoskeletal events (15.4% each). No patient developed human antihuman antibody, even after multiple doses. No ≥3 Grade immune-related adverse events (irAE) occurred in the 28-day period following the first dose of nivolumab. On repeat dosing, four patients experienced an irAE; Grade 3 colitis (one patient), Grade 2 hypothyroidism (one patient),

and Grade 2 polyarticular arthropathies (two patients) [17]. In the subsequent Phase 1 multiple ascending dose study (1, 3, and 10 mg/kg), an irAE of any grade was reported in 24/106 patients (22.6%) [16]. Most commonly observed were pruritus (9.4%), rash (8.5%), and diarrhea (7.5%). Other reported irAEs included uveitis (one patient), hypothyroidism (one patient) and elevated thyroid-stimulating hormone (two patients). The most common non-irAE was fatigue (13.2%). Of note, no apparent dose-safety relationship was observed in either of the two reported Phase 1 studies [16, 17].

Nivolumab has demonstrated anti-tumor efficacy against patients with NSCLC. A total of 122 previously treated patients with NSCLC were evaluable after treatment with nivolumab at three different doses. Of patients with squamous histology, 0/13 responders were observed at 1 mg/kg Q2W, 4/15 (27%) responders were observed at 3 mg/kg Q2W, and 5/20 (25%) responders were observed at 10 mg/kg Q2W. Among patients with non-squamous histology, 1/18 (6%) responder was observed at 1 mg/kg Q2W, 5/18 (28%) responders were observed at 3 mg/kg Q2W, and 5/37 (14%) responders were observed at 10 mg/kg Q2W [78]. These results warrant further study of anti-PD-1 therapy in patients with NSCLC.

Pembrolizumab (MK-3475) (previously known as SCH 900475) is a potent and highly selective humanized mAb of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Both (MK-3475) and nivolumab contain the S228P stabilizing mutation and have no antibody-dependent cell-mediated cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC) activity. Pembrolizumab (MK-3475) strongly enhances T lymphocyte immune responses in cultured blood cells from healthy human donors, cancer patients, and primates. In T cell activation assays using human donor blood cells, the EC50 was in the range of 0.1 to 0.3 nM. Pembrolizumab (MK-3475) also modulates the level of interleukin-2 (IL-2), tumor necrosis factor alpha (TNFα), interferon gamma (IFNγ), and other cytokines. The antibody potentiates existing immune responses only in the presence of antigen and does not nonspecifically activate T cells.

Preliminary data from the dose escalation of Part A warrants continuation of investigation. In dose escalation cohort, 9 patients (3 at each dose level) completed the dose-limiting toxicity (DLT) period (28 days). Patients had non-small cell lung cancer (NSCLC, n=3), rectal cancer (n=2), melanoma (MEL, n=2), sarcoma (n=1), or carcinoid (n=1). To date, no patient has experienced a DLT. Drug-related AEs across all doses in Part A included Grade 1 fatigue (n=3), nausea (n=2), diarrhea (n=1), dysgeusia (n=1), breast pain (n=1), and pruritus (N=1). One drug-related Grade 2 AE of pruritus was reported. There were no drug-related severe AEs (G3-5). PK data are shown in Table 3-1 indicating a long half-life of pembrolizumab (MK-3475) (>14 days). Peripheral target engagement (measured by ex vivo IL-2 production assay) was observed starting at 1 mg/kg without dose response. IL-2 release assay data also suggested that target engagement was durable for >21 days. Two patients with MEL had a partial response by RECIST 1.1 and remained on therapy >6 months. Objective evidence of tumor size reduction per volumetric imaging analysis (but stable disease by RECIST 1.1) was observed in three additional patients with advance cancer (1 MEL and 2 NSCLC). The

Part A data set described above also warranted the more comprehensive investigation of pembrolizumab (MK-3475).

Table 3-1

Mean (CV%) PK Parameter Values of pembrolizumab (MK-3475) Following a Single IV Dose of 1, 3 or 10 mg/kg in Cycle 1

Dose (mg/kg)	N	Cmax (μg/mL)	AUC(0-28day) (μg·day /mL)	$t_{1/2}$ [1] (day)
1	4	16.8 (23)	163 (20) [2]	15.1 (41) [2]
3	3	109 (26)	990 (23)	21.7 (11)
10	2	337 (8)	2640 (30)	13.6 (28)

1 PK sampling up to 28 days following first IV administration, $t_{1/2}$ therefore not yet fully characterized
2 N=3 due to subject discontinuation

Data from Part B was presented at the Society of Melanoma Research in November 2012. Safety analysis on 132 patients revealed most adverse events to be grades 1-2. The most commonly reported AEs were fatigue (28%), nausea (23%), rash (22%), diarrhea (20%) and cough (19%). The most commonly reported drug-related AEs were fatigue (22%), rash (18%), diarrhea (14%), pruritus (14%), and arthralgia (11%). Of note, pneumonitis (all Gr 1-2) was noted at a rate of 3% amongst patients with melanoma. Grade 3-5 AEs occurred in 27% of patients, of which 9% were considered drug-related. Of note, preliminary safety data from patients with NSCLC appears similar to that in melanoma, with the exception that the rate of pneumonitis is about 8%. Preliminary efficacy analyses on the first 85 malignant melanoma patients that were dosed with pembrolizumab (MK-3475) revealed an objective response rate (confirmed + unconfirmed) of 51% by irRC (immune related response criteria) and 47% by RECIST. Confirmed responses amongst all major NSCLC histologies have been observed in Part C.

Two recent Phase III studies of the anti-CTLA4 mAb ipilimumab have shown statistically significant improvement of overall survival in patients with stage IV melanoma [71, 72]. At the same time, the BRAF inhibitor vemurafenib has shown significant survival improvement compared to chemotherapy with DTIC in patients with stage IV melanoma harboring mutant BRAF [73]. Despite that encouraging progress, melanoma patients overall outlook remains bleak, and the development of new agents is warranted to further improve clinical outcome benefit. Based on the preliminary clinical data, PD-1 inhibitors such as pembrolizumab (MK-3475) appear to be attractive candidates for pursuing that goal.

An important objective of the present study is the investigation of biomarkers in tumor tissue which may be able to identify which melanoma and NSCLC patients have a high probability to benefit from treatment with pembrolizumab (MK-3475) and which do not. Therefore, Parts B, C, D and F of the study will mandate pretreatment tumor biopsies.

The study will also collect tumor biopsies while on treatment and post treatment, as changes in biomarkers compared to baseline may provide meaningful insights into characteristics associated with sensitivity or resistance to pembrolizumab (MK-3475).

Analysis of retrospective data correlating a high PD-L1 expression in patients with NSCLC with poor overall survival raises the possibility that these patients may be likely to benefit significantly from pembrolizumab (MK-3475). In fact, in the Ph 1 study of single dose nivolumab, 1 out of 11 patients with NSCLC (9%) who were previously treated demonstrated a partial response to single agent nivolumab. That patient was treated for at least 14 months [16]. Recent publication of the multi-dose nivolumab monotherapy trial revealed that of the 25 patients with PD-L1 expression in the tumor, nine patients responded, compared with no responders from the 17 patients who did not express PD-L1 on their tumor [76]. Given the poor outcomes of patients with metastatic NSCLC, more therapies are needed to prolong survival. Preliminary data from Part C suggests that those previously treated patients with a high PD-L1 expression on their tumor are more likely to respond to pembrolizumab (MK-3475).

3.1.3 Rationale for Dose

With Amendment 10 the dose of pembrolizumab (MK-3475) is 200 mg Q3W for all study parts. Based on the totality of data generated in the KEYTRUDA development program, 200 mg Q3W is the appropriate dose of pembrolizumab across all indications and regardless of tumor type. Further information on the rationale for selecting 200 mg Q3W is summarized below.

Clinical data showed meaningful improvement in benefit-risk including overall survival at 200 mg Q3W across multiple indications, and pharmacology data showed full target saturation in both systemic circulation (inferred from PK data) and tumor (inferred from physiologically based pharmacokinetic [PBPK] analysis) at 200 mg Q3W.

Among the 8 randomized dose-comparison studies, a total of 2262 subjects were enrolled with melanoma and NSCLC, covering different disease settings (treatment naïve, previously treated, PD-L1 enriched and all-comers) and different treatment settings (monotherapy and in combination with chemotherapy). Five studies compared 2 mg/kg Q3W vs. 10 mg/kg Q3W (KEYNOTE-001 B2, KEYNOTE-001 D, KEYNOTE-002, KEYNOTE-010 and KEYNOTE-021), and three studies compared 10 mg/kg Q3W vs. 10 mg/kg Q2W (KEYNOTE-001 B3, KEYNOTE-001 F2 and KEYNOTE-006). All of these studies demonstrated flat dose- and exposure-response relationships across the doses studied representing an approximate 5- to 7.5-fold difference in exposure. The 2 mg/kg (or 200 mg fixed-dose) Q3W provided similar responses to the highest doses studied. Subsequently, flat dose-/exposure-response relationships were also observed in other tumor types including head and neck cancer, bladder cancer, gastric cancer and classical Hodgkin Lymphoma, confirming 200 mg Q3W as the appropriate dose independent of the tumor type. These findings are consistent with the mechanism of action of pembrolizumab, which acts by interaction with immune cells, and not via direct binding to cancer cells.

Additionally, pharmacology data clearly show target saturation at 200 mg Q3W. First, PK data in KN001 evaluating target-mediated drug disposition (TMDD) conclusively demonstrated saturation of PD-1 in systemic circulation at doses much lower than 200 mg Q3W. Secondly, a PBPK analysis was conducted to predict tumor PD-1 saturation over a wide range of tumor penetration and PD-1 expression. This evaluation concluded that pembrolizumab at 200 mg Q3W achieves full PD-1 saturation in both blood and tumor.

Finally, population PK analysis of pembrolizumab, which characterized the influence of body weight and other subject covariates on exposure, has shown that the fixed-dosing provides similar control of PK variability as weight based dosing, with considerable overlap in the distribution of exposures from the 200 mg Q3W fixed dose and 2 mg/kg Q3W dose. Supported by these PK characteristics, and given that fixed-dose has advantages of reduced dosing complexity and reduced potential of dosing errors, the 200 mg Q3W fixed-dose was selected for evaluation across all pembrolizumab protocols.

3.1.4 Planned Exploratory Biomarker Research

Cytotoxic T cells recognize tumor cells by binding to peptide loaded HLA class I complex. There are a number of immunodominant peptides that are loaded onto specific HLA haplotypes and the frequency of HLA alleles varies in populations. 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.

In addition, the Sponsor may explore how tumor response correlates with PD-1 expression within the tumor, PD-L2 expression within the tumor, or an immune signature.

Tumor and blood samples may undergo additional proteomic, genomic and transcriptional analyses (both DNA and RNA analyses). This additional biomarker or genomic research may be conducted to identify factors important for pembrolizumab (MK-3475) therapy and patient response to therapy (for example, to identify risk factors for adverse events or who might best respond to treatment).

3.1.5 Rationale for Future Biomedical Research

The Sponsor will conduct Future Biomedical Research on DNA (blood) and leftover tumor biopsy specimens collected during this clinical trial. This research may include genetic analyses (DNA), gene expression profiling (RNA), proteomics, metabolomics (serum, plasma) and/or the measurement of other analytes. Specimens may be used for future assay development.

Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol (as part of the main trial) and will only be conducted on specimens from appropriately consented subjects. The objective of collecting specimens for Future Biomedical Research is to explore and identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments. For instance,

exploratory pharmacogenetics (PGt) studies may be performed if significant Pharmacokinetic/Pharmacodynamic (PK/PD) relationships are observed or adverse events are identified. Genomic markers of disease may also be investigated. Such retrospective pharmacogenetic studies will be conducted with appropriate biostatistical design and analysis and compared to PK/PD results or clinical outcomes. Any significant PGt relationships to outcome would require validation in future clinical trials. The overarching goal is to use such information to develop safer, more effective drugs, and/or to ensure that subjects receive the correct dose of the correct drug at the correct time. The details of this Future Biomedical Research sub-trial are presented in Appendix 6.6: Collection and Management of Specimens for Future Biomedical Research. Additional informational material for institutional review boards/ethics committees (IRBs/ERCs) and investigational site staff is provided in Appendix 7.

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 (NSCLC), immunotherapy, anti-neoplastic biological therapy or investigational agents other than pembrolizumab (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, H1N1 flu, rabies, BCG, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however intranasal influenza vaccines (e.g. Flu-Mist) are live attenuated vaccines, and are not allowed."

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

For melanoma patients participating in Parts A, B or D, local surgery or radiation, if indicated for palliative measures, may be permitted beyond or after the Week 12 tumor assessment only after discussion for approval by the Sponsor. If such local therapy occurs, the patient may continue to receive treatment with pembrolizumab (MK-3475) after discussion and approval by the Sponsor if the investigator believes that it is in the patient's best interest. Response assessments must continue every 12 weeks (+/- 7 days) from C1D1 if the patient continues to receive study medication.

For lung patients participating in Parts C and F, local surgery or radiotherapy to any tumor lesion is prohibited during first 27 weeks of the trial. After week 27 tumor assessment, local surgery or radiation, if indicated for palliative measures, may be permitted only after discussion for approval by the Sponsor. If such local therapy occurs, the patient may continue to receive treatment with pembrolizumab (MK-3475) after discussion and approval by the Sponsor if the investigator believes that it is in the patient's best interest. Response assessments must continue as outlined in the flow chart from C1D1 if the patient continues to receive study medication.

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 monthly as per local regulations where applicable. 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

Pembrolizumab (MK-3475) may have adverse effects on a fetus in utero. Furthermore, it is not known if pembrolizumab (MK-3475) has transient adverse effects on the composition of sperm.

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

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

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

OR

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

OR

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

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

(1) practice abstinence† from heterosexual activity;

OR

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

Acceptable methods of contraception are‡:

Single method (one of the following is acceptable):

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

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

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

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

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

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study subjects of childbearing potential must adhere to the contraception requirement (described above) from the day of study medication initiation (or 14 days

prior to the initiation of study medication for oral contraception) throughout the study period up to 120 days after the last dose of trial therapy. If there is any question that a subject of childbearing potential will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

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

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 participant inadvertently becomes pregnant while on treatment with pembrolizumab, the participant will be immediately discontinued from study treatment. The site will contact the participant at least monthly and document the participant'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 (eg, death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor. If a male participant impregnates his female partner, the study personnel at the site must be informed immediately and the pregnancy must be reported to the Sponsor and followed as described in Section 3.4.4.

3.2.4.4 Use in Nursing Women

It is unknown whether pembrolizumab (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 pembrolizumab (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.

Note: As of Amendment 11, PK samples are no longer being collected (see Section 3.3.2).

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.

3.2.5.4.3 Guidelines for Study Drug Administration

With Amendment 10, all subjects will receive fixed dose 200 mg Q3W.

Pembrolizumab (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).

The rationale for previous dosing regimen can be found in Amendment 09.

Study treatment will continue until disease progression or unacceptable toxicity or tolerability. Patients with documented disease progression may continue treatment, if the physician believes patient will benefit (with sponsor consultation).

3.2.5.4.4 Guidelines for Dose Modifications

Dose modification and toxicity management for immune-related AEs associated with pembrolizumab

AEs associated with pembrolizumab exposure may represent an immunologic etiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than one

body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab and administer corticosteroids. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab are provided in **Table 3-2**.

Table 3-2 Dose Modification and Toxicity Management Guidelines for Immune-related AEs Associated with Pembrolizumab

General instructions:

1. Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks.
2. For situations where pembrolizumab has been withheld, pembrolizumab can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered. Pembrolizumab should be permanently discontinued if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks.
3. For severe and life-threatening irAEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.

Immune-related AEs	Toxicity grade or conditions (CTCAEv4.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
Pneumonitis	Grade 2	Withhold.	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper.	• Monitor participants for signs and symptoms of pneumonitis. • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment. • Add prophylactic antibiotics for opportunistic infections.
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue.		
Diarrhea / Colitis	Grade 2 or 3	Withhold.	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper.	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus). • Participants with ≥Grade 2 diarrhea

	Grade 4	Permanently discontinue.		suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
AST / ALT elevation or Increased bilirubin	Grade 2	Withhold.	• Administer corticosteroids (initial dose of 0.5-1 mg/kg prednisone or equivalent) followed by taper.	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable.
	Grade 3 or 4	Permanently discontinue.	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper.	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold.	• Initiate insulin replacement therapy for participants with T1DM. • Administer anti-hyperglycemic in participants with hyperglycemia.	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes.
Hypophysitis	Grade 2	Withhold.	• Administer corticosteroids and initiate hormonal replacements as clinically indicated.	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency).
	Grade 3 or 4	Withhold or permanently discontinue. [1]		
Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate.	• Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or permanently discontinue. [1]		
Hypothyroidism	Grade 2-4	Continue.	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyroinine) per standard of care.	• Monitor for signs and symptoms of thyroid disorders.

Nephritis and Renal dysfunction	Grade 2	Withhold.	• Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper.	• Monitor changes of renal function.
	Grade 3 or 4	Permanently discontinue.		
Myocarditis	Grade 1 or 2	Withhold.	• Based on severity of AE administer corticosteroids.	• Ensure adequate evaluation to confirm etiology and/or exclude other causes.
	Grade 3 or 4	Permanently discontinue.		
All other immune-related AEs	Intolerable/ persistent Grade 2	Withhold.	• Based on type and severity of AE administer corticosteroids.	• Ensure adequate evaluation to confirm etiology and/or exclude other causes.
	Grade 3	Withhold or discontinue based on the type of event. Events that require discontinuation include and not limited to: Guillain-Barre Syndrome, encephalitis.		
	Grade 4 or recurrent Grade 3	Permanently discontinue.		

1. Withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician.

NOTE:
For participants with Grade 3 or 4 immune-related endocrinopathy where withhold of pembrolizumab is required, pembrolizumab may be resumed when AE resolves to ≤ Grade 2 and is controlled with hormonal replacement therapy or achieved metabolic control (in case of T1DM).

Dose modification and toxicity management of infusion-reactions related to pembrolizumab

Pembrolizumab may cause severe or life threatening infusion-reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab associated infusion reaction are provided in Table 3-3.

Table 3-3 **Pembrolizumab Infusion Reaction Dose Modification and Treatment Guidelines**

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (eg, from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose. **Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment**	Participant may be premedicated 1.5 h (± 30 minutes) prior to infusion of pembrolizumab with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500 to1000 mg po (or equivalent dose of analgesic).

Grades 3 or 4 Grade 3: Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: Epinephrine** IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Oxygen Pressors Corticosteroids Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated.	No subsequent dosing
In cases of anaphylaxis, epinephrine should be used immediately. **Participant is permanently discontinued from further study drug treatment. Note: Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE) at http://ctep.cancer.gov		

Other Allowed Dose Interruption for Pembrolizumab

Pembrolizumab may be interrupted for situations other than treatment-related AEs such as medical / surgical events or logistical reasons not related to study therapy. Participants should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the patient's study record.

3.2.5.4.4.1 Adverse Events of Special 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. Selected irAEs are defined as Adverse Events of Special Interest (AEOSI) and must be reported to the Sponsor. A list of AEOSI is provided in the *Pembrolizumab AEOSI Preferred Term List* document. AEOSIs should be entered in the database if they are considered drug related. Refer to the Data Entry Guidelines (DEGs) for instructions.

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.

3.2.5.4.5 Duration of Therapy

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

- Documented disease progression, unless physician believes patient will benefit from continued treatment (with sponsor consultation)
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse experiences (see Section 3.2.5.4.4)
- 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 pembrolizumab (MK-3475) treatment for at least 6 months may discontinue pembrolizumab (MK-3475) treatment at the discretion of the investigator. See Section 1.6.
- Patients who have confirmed SD or PR, may discontinue after 2 years of treatment with pembrolizumab (MK-3475)

If a patient discontinues from the study, the procedures will be followed as described in Section 3.2.5.4.7 and 3.2.5.4.8.

Upon study completion, participants are discontinued and enrolled in a separate extension study, see Section 1.4.

3.2.5.4.6 Safety Follow-up Visit

The mandatory Safety Follow-up Visit should be conducted approximately 30 days after the last dose of trial treatment or before the initiation of a new anticancer treatment, whichever comes first. 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.

All AEs that occur prior to the Safety Follow-Up Visit should be recorded. Subjects with an AE of Grade >1 will be followed until the resolution of the AE to Grade 0 to 1 or until the beginning of a new anticancer therapy, whichever occurs first. Serious AEs that occur within 90 days of the end of treatment or before initiation of a new anticancer treatment should also be followed and recorded.

Patients who are eligible for retreatment with pembrolizumab (MK-3475) (as described in Section 3.2.5.4.9) may have up to two safety follow-up visits, one after the Treatment Period and one after the Second Course Phase.

3.2.5.4.7 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 Parts A, 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 SD or PR or 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, SD, PR 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 pembrolizumab (MK-3475) according to the criteria in Section 3.2.5.4.9 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).

3.2.5.4.8 Survival Follow-up

Subjects who move into the Survival Follow-up Phase should be contacted by telephone approximately every 90 days ± 28 days to assess for survival status until death, withdrawal of consent, or the end of the trial, whichever occurs first. Refer to the Study Flow Chart (Section 1.7; Parts B, C, D, and F: Follow-up.

3.2.5.4.9 Second Course Phase

Patients may be eligible to receive pembrolizumab (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 pembrolizumab (MK-3475) after attaining an investigator-determined confirmed CR according to irRC
- Stopped initial treatment with pembrolizumab (MK-3475) after attaining investigator-determined confirmed SD, or PR, after 2 years of treatment with pembrolizumab (MK-3475)
- Was treated for at least 24 weeks with pembrolizumab (MK-3475) before discontinuing therapy
- Experienced an investigator-determined progression after stopping their initial treatment with pembrolizumab (MK-3475)

- Did not receive any other systemic anti-cancer treatment since the last dose of pembrolizumab (MK-3475); (local treatment such as radiation or surgery as anti-cancer therapy is allowed; Sponsor consultation must be obtained and subjects should have recovered completely from side effects of local procedures. In patients with brain metastases, neurological stability must be documented before initiating pembrolizumab.)
- 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 subjects of childbearing potential must be willing to use an adequate method of contraception as outlined in Section 3.2.4.2 – Contraception, for the course of the study through 120 days after the last dose of study medication.
- Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject.
- Male subjects of childbearing potential must agree to use an adequate method of contraception as outlined in Section 3.2.4.2 - Contraception, starting with the first dose of study therapy through 120 days after the last dose of study therapy.
- Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject. 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 are encouraged to obtain a biopsy before receiving pembrolizumab (MK-3475) in second course phase.

Patients who restart treatment will be retreated at the 200 mg every 3 week dose and schedule of pembrolizumab (MK-3475).

3.2.5.5 Survival Status

To ensure current and complete survival data is available at the time of database locks, updated survival status and its respective entry into the database may be requested during the course of the study by the Sponsor. For example, updated survival status may be requested prior to but not limited to an external Data Monitoring Committee (eDMC) review, interim and/or final analysis. Upon Sponsor notification, all participants who do not/will not have a scheduled study visit or study contact during the sponsor defined time period will be contacted for their survival status (excluding participants that have previously recorded a death event in the collection tool).

3.2.5.6 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.

3.2.5.7 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. A subject may discontinue from study treatment but should continue to be followed up for survival. 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.

Discontinuation of study treatment does not represent withdrawal from the study.

3.2.5.8 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.

With Amendment 10, imaging will be investigator assessed only. Imaging will not be assessed by central imaging vendor. Subjects may obtain scans locally.

3.3.1.1 Response Criteria

For Parts A, B, C, D and F, tumor response will be determined by investigator assessment.

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 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 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 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 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.

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 pembrolizumab (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.

Parts A, B, and D:

Tumor imaging will be performed approximately every 16 weeks (112 days) (±28 days) from the first dose of study medication through Year 3, and then Q6 months (24 weeks) (+/- 28 days) through Years 4 and 5. After 5 years, imaging will be performed annually or per institutional standard of care. Response status will be assessed by the study site. Refer to Section 3.3.1.3 of the protocol for additional information. The same imaging technique must be used in a patient throughout the study. After first documentation of response or progression, repeat imaging will be required approximately 4 weeks later for confirmation, as per immune related response criteria (irRC) guidelines (see Appendix 6.5) (see Section 2.4.1).

Parts C and F:

Tumor imaging will be performed approximately every 9 weeks (63 days) (±28 days) from the first dose of study medication through Year 2, then Q16 weeks (112 days) (±28 days) through Year 3, and Q6 months (24 weeks) (±28 days) through Years 4 and 5. After 5 years, imaging will be performed annually or per institutional standard of care. Response status will be assessed by the study site. 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. The same imaging technique must be used in a patient throughout the study. After first documentation of response or progression, repeat imaging will be required approximately 4 weeks later for confirmation, as per immune related response criteria (irRC) guidelines (see Appendix 6.5) (see Section 2.4.1).

Parts A, B, D, C, and F

If imaging 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 to 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 pembrolizumab (MK-3475) will continue/ resume per imaging schedule. If repeat imaging confirms PD, patients will be discontinued from study therapy or permitted to continue treatment if the investigator believes patient is deriving benefit with sponsor consultation. This clinical judgment decision by the site should be based on the subject's overall clinical condition, including the following parameters:

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

2) No decline in ECOG performance status

3) Absence of rapid progression of disease

4) Absence of progressive tumor at critical anatomical sites (e.g., cord compression) requiring urgent alternative medical intervention

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

3.3.2 Pharmacokinetic Measurements

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

PK samples will be collected every 4 cycles and 30 days after discontinuation of study drug (or until the subject starts new cancer therapy). All pre-dose trough samples should be drawn within 24 hours before infusion of pembrolizumab.

The accumulation of robust PK and ADA data has allowed for the adequate characterization the clinical pharmacology of pembrolizumab across indications. With Amendment 10 ADA samples were no longer collected. Upon approval of Amendment 11 each site will stop the collection of PK samples for all subjects. Blood samples for PK and ADA may be stored. Analysis will be performed only if required.

3.3.3 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 (genomic research) in biopsy tissue and blood samples
- 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., CBC, serum chemistries, thyroid function,) 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 events may occur during clinical trials, or as prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

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

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

From the time of treatment allocation/randomization through 30 days following cessation of treatment, all serious adverse events and drug related AEOSI must be reported by the investigator. Such events will be recorded at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in section 3.4.5.1. The investigator will make every attempt to follow all subjects with non-serious adverse events for outcome.

With Amendment 10, investigators are required to report drug related NSAEs if they meet criteria for AEOSI (refer to the *Pembrolizumab AEOSI Preferred Term List* document) or are ECIs described in Section 3.4.8 below. Previous ECI guidance is now updated in Amendment 10 and is no longer required to be reported to Merck safety group. Other NSAEs do not need to be reported.

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

3.4.3 Definition of an Overdose for This Protocol

For purposes of this trial, an overdose will be defined as any dose exceeding the prescribed dose for pembrolizumab (MK-3475) by ≥1000 mg (5 times the dose). No specific information is available on the treatment of overdose of pembrolizumab (MK-3475). In the event of overdose, pembrolizumab (MK-3475) should be discontinued

and the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

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

All reports of overdose with and without an adverse event must be reported by the investigator within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

3.4.4 Reporting of Pregnancy to SPONSOR

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

Pregnancies and lactations that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure. Pregnancies and lactations that occur from the time of treatment allocation/randomization through 120 days following cessation of Sponsor's product, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, must be reported by the investigator. All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

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:

- Results in death;
- Is life threatening;
- Results in persistent or significant disability/incapacity;
- Results in or prolongs an existing inpatient hospitalization;
- Is a congenital anomaly/birth defect;
- Is an other important medical event

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

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

Refer to Table 3-4 for additional details regarding each of the above criteria.

For the time period beginning when the consent form is signed until treatment allocation/randomization, any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study (reference Section 3.4.5.1 for additional details), that occurs to any subject must be reported within 24 hours to the Sponsor if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study (reference Section 3.4.5.1 for additional details), whether or not related to the Sponsor's product, must be reported within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent)

Additionally, any serious adverse event, considered by an investigator who is a qualified physician to be related to the Sponsor's product that is brought to the attention of the

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

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

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 3-4 for instructions in evaluating adverse experiences.

Table 3-4 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 re-exposed 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

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be reported to the Sponsor.

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

For the time period beginning at treatment allocation/randomization through 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, any ECI, or follow up to an ECI, whether or not related to the Sponsor's product, must be reported within 24 hours to the Sponsor, either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

Events of clinical interest for this trial include:

1. An overdose of Sponsor's product, as defined in Section 3.4.3 and 3.4.3.1 - Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor, that is not associated with clinical symptoms or abnormal laboratory results.

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

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

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 if the events are considered drug related. 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 pembrolizumab (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 3-5) 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 3-5

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 pembrolizumab (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 pembrolizumab (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 or death. 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 pembrolizumab (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 pembrolizumab (MK-3475) and analysis of target engagement will be obtained at the time points listed in the Study Flow Chart, Section 1.7.

As of Amendment 11, blood samples for serum levels of pembrolizumab (MK-3475) and analysis of target engagement will not be collected (see Section 3.3.2).

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 pembrolizumab (MK-3475) in Cycle 1 and completed all safety evaluations up to and including at least 28 days after the first administration of pembrolizumab (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 analyses 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.

As of Amendment 11, pharmacokinetic and pharmacodynamic analyses will not be performed (see Section 3.3.2).

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

Pembrolizumab (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 analysis 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.

Note: As of Amendment 11, pharmacokinetic analyses will not be performed (see Section 3.3.2).

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.

Note: As of Amendment 11, PK analyses will not be performed (see Section 3.3.2).

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 ipilimumab-naïve patients at 2 mg Q3, 22 ipilimumab-naïve patients at 10 mg Q3, 41 ipilimumab-naïve patients at 10 mg Q2, 32 ipilimumab-treated patients at 10 mg Q3, and 16 ipilimumab-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 pembrolizumab (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 pembrolizumab (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 ipilimumab-refractory population and the ipilimumab-naïve population. Based upon current data from this trial indicating similar response rates between ipilimumab-naïve and ipilimumab-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 ($\leq$ 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 $\geq$ 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 PD data will inform the determination of a recommended Phase 2 dose.

Note: As of Amendment 11, PK analyses will not be performed (see Section 3.3.2).

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 pembrolizumab (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 pembrolizumab (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 pembrolizumab (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 pembrolizumab (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 ipilimumab-refractory population and the ipilimumab-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 to 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 ipilimumab-naïve vs non ipilimumab-naive. Based on preliminary data from non-randomized patients, the RR appears similar between the non ipilimumab-naive population and the ipilimumab-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 pembrolizumab (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 (single arm)

With 40 patients treated at 2 mg/kg Q3W, 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 30%. A p-value of 2.5% approximately corresponds to an empirical RR of 22.5% (9/40).

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 pembrolizumab (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 pembrolizumab (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 3-6 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 3-6

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 3-7 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 pembrolizumab (MK-3475). A Hochberg procedure with type I error rate of 5% (one-sided) will be applied to assist with the analysis.

Table 3-7

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

Pembrolizumab (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 3-8.

Table 3-8

Product Descriptions

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

3.6.3 Primary Packaging and Labeling Information

Pembrolizumab (MK-3475) (SCH900475) supplies will be packaged in **glass vials** as described in Table 3-9 below.

Table 3-9

Packaging of Clinical Supplies

Product Name & Potency	Fill Count	Dosing Instructions
Pembrolizumab (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. All used vials should be properly disposed of immediately in biohazard bins. Unused or expired vials 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 investigatir 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 Amendments Act (FDAAA) of 2007 and the European Medicines Agency (EMA) clinical trial Directive 2001/20/EC, the Sponsor of the study is solely responsible for determining whether the study and its results are subject to the requirements for submission to http://www.clinicaltrials.gov, www.clinicaltrialsregister.eu or other local registries. Merck, as Sponsor of this study, will review this protocol and submit the information necessary to fulfill these requirements. Merck entries are not limited to FDAAA or the EMA clinical trial directive mandated trials. Information posted will allow participants to identify potentially appropriate studies 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 obligations under FDAAA, the EMA clinical trials directive or other locally mandated registries are that of the Sponsor and agrees not to submit any information about this study or its results to those registries.

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.

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6. APPENDICES

6.1 LABORATORY SAFETY TESTS/SCREENING/BASELINE LABS

The laboratory tests listed below will be performed only by the local study site lab. Patient treatment and overall management decisions will be based on local lab data.

Hematology

White Blood Cell Count (total and differential)
Absolute Neutrophil Count
Absolute Lymphocyte Count
Red Blood Cell Count
Hemoglobin
Hematocrit
Platelets

Coagulation

PT (INR)
aPTT

Comprehensive Chemistry Panel

Sodium
Potassium
Chloride
Calcium
Phosphorus
Magnesium
Carbon Dioxide (CO_2 or bicarbonate)
Urea Nitrogen (BUN)
Creatinine
Uric acid
Protein, total
Albumin
Bilirubin, total
Alkaline Phosphatase
Alanine aminotransferase (ALT)
Aspartate aminotransferase (AST)
Lactate dehydrogenase (LDH)
Bilirubin, direct and indirect
Glucose
Cholesterol, total
Triglycerides

Other

Urine and serum beta-HCG (for women of child bearing potential only)
Part A only - Serum tumor markers (if and as applicable for a given tumor type)

Analysis will be performed by the local study site laboratory where feasible. If not feasible, tests will be performed by a central laboratory.

CEA, CA 15-3, CA-125, AFP, PSA, β-hCG, CA 19-9

6.2 ECOG PERFORMANCE STATUS

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

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

6.3 RESPONSE EVALUATION CRITERIA IN SOLID TUMORS (RECIST) 1.1 CRITERIA FOR EVALUATING RESPONSE IN SOLID TUMORS

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

* As published in the European Journal of Cancer:

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

In addition, volumetric analysis will be used for response assessment (so-called enhanced RECIST)

6.4 COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS V4.0 (CTCAE)

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

6.5 IMMUNE RELATED RESPONSE CRITERIA

For all patients who experience disease progression on study, the date noted for of disease progression is the time of the scan where it is originally detected, and not the following date of the confirmatory scan.

Definitions of measurable and non-measurable disease

Measurable disease: Neoplastic masses that can be precisely measured in 2 in-plane perpendicular diameters. Both its longest diameter and its longest perpendicular must be greater than or equal to 10 mm or 2 times the axial slice thickness if the slice thickness is greater than 5 mm. Lymph nodes must have a short-axis line-length of ≥15 mm. Malignant lymph nodes must be measurable in 2 perpendicular diameters. Both its longest diameter and its longest perpendicular must be greater than or equal to 15 mm. The quantitative endpoint will be defined as the product of the longest diameter with its longest perpendicular.

Non-measurable disease: Non-measurable lesions are those that are not suitable for quantitative assessment over time. These include:

1) Neoplastic masses that are too small to measure, because their longest uninterrupted diameter or longest perpendicular are less than 10 mm.

2) Neoplastic masses whose boundaries cannot be distinguished. This includes masses which cannot be demarcated from surrounding tissue because of inadequate contrast, masses with overly complex morphology, or those with highly heterogeneous tissue composition.

3) Other types of lesions that are confidently felt to represent neoplastic tissue, but difficult to quantify in a reproducible manner. These include bone metastases, leptomeningeal metastases, malignant ascites, pleural/pericardial effusions, inflammatory breast disease, lymphangitis cutis/pulmonis, cystic lesions, ill-defined abdominal masses, etc.

For irRC, only target lesions selected at baseline and measurable new lesions are taken into account.

At the baseline tumor assessment, the sum of the products of the two largest perpendicular diameters (SPD) of all **index lesions** (five lesions per organ, up to 10 visceral lesions and five cutaneous index lesions) is calculated.

At each subsequent tumor assessment, the SPD of the index lesions and of new, measurable lesions (≥10 X 10 mm; up to 5 new lesions per organ: 5 new cutaneous lesions and 10 visceral (non-cutaneous) lesions) are added together to provide the total time-point **tumor burden**.

Overall response using irRC:

- **Complete Response (irCR):** Complete disappearance of all tumor lesions (whether measureable or not, and no new lesions). CR must be confirmed by repeated, consecutive assessments made no less than 4 weeks from the date first documented.

- **Partial Response (irPR):** Decrease in SPD of 50% or greater by a consecutive assessment at least 4 weeks after first documentation.

- **Stable Disease (irSD):** Failure to meet criteria for irCR or irPR, in absence of irPD.

- **Progressive Disease (irPD):** At least 25% increase in SPD relative to nadir (minimum recorded tumor burden) Confirmation by a repeat, consecutive assessment no less than 4 weeks from the data first documented.

Please note other key differences between irRC and the original WHO criteria:

New measurable lesions will be incorporated into the SPD

New non measurable lesions do not define progression but preclude irCR

Non-index lesions contribute to defining irCR (complete disappearance required).

See the Investigators Imaging Operations Manual (IIOM) for more details)

REFERENCE

IrRC for the current protocol is adopted from the following reference:

Wolchok, JD, Hoos, A, O'Day S, et al., Guidelines for the Evaluation of Immune Therapy Activity in Solid Tumors: Immune-Related Response Criteria. Clinical Cancer Research, 2009 Dec 1;15(23):7412-20. Epub 2009 Nov 24.

6.6 COLLECTION AND MANAGEMENT OF SPECIMENS FOR FUTURE BIOMEDICAL RESEARCH

6.6.1 Scope of Future Biomedical Research

The DNA and leftover tumor tissue specimen(s) collected in the current trial will be used to study various causes for how subjects may respond to a drug. The DNA and leftover tumor tissue specimen(s) will be stored to provide a resource for future studies conducted by Merck focused on the study of biomarkers responsible for how a drug enters and is removed by the body, how a drug works, other pathways a drug may interact with, or other aspects of disease.

It is now well recognized that information obtained from studying and testing clinical specimens offers unique opportunities to enhance our understanding of how individuals respond to drugs, enhance our understanding of human disease and ultimately improve public health through development of novel treatments targeted to populations with the greatest need. All specimens will be used by Merck or designees and research will be monitored and reviewed by a committee of our scientists and clinicians.

6.6.2 Definitions

a. Biomarker: A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition.[1]

b. Pharmacogenomics: The investigation of variations of DNA and RNA characteristics as related to drug response.[2]

c. Pharmacogenetics: A subset of pharmacogenomics, pharmacogenetics is the influence of variations in DNA sequence on drug response.[2]

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

6.6.3 Summary of Procedures for Future Biomedical Research

a. Subjects for Enrollment

All subjects enrolled in the clinical trial will be considered for enrollment in the Future Biomedical Research sub-study.

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[1] National Cancer Institute: http://www.cancer.gov/dictionary/?searchTxt=biomarker

[2] International Conference on Harmonization: Definitions For Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories - E15; http://www.ich.org/LOB/media/MEDIA3383.pdf.

b. Informed Consent

Informed consent for specimens (i.e., DNA, RNA, protein, etc) will be obtained during screening for protocol enrollment from all subjects or legal guardians, at a study visit by the investigator or his or her designate. Informed consent for Future Biomedical Research should be presented to the subjects on Visit 1. If delayed, present consent at next possible Subject Visit. Informed consent must be obtained prior to collection of all Future Biomedical Research specimens.

Subjects are not required to participate in the Future Biomedical Research sub-study in order to participate in the main trial.

Consent forms signed by the subject will be kept at the clinical trial site under secure storage for regulatory reasons. Information contained on the consent form alone cannot be traced to any specimens, test results, or medical information once the specimens have been rendered de-identified. Subjects who decline to sign the Future Biomedical Research informed consent will not have the specimen collected nor will they be discontinued from the main study.

A template of each study site's approved informed consent will be stored in the Sponsor's clinical document repository. Each consent will be assessed for appropriate specimen permissions.

Each informed consent approved by an ethics committee is assigned a unique tracking number. The tracking number on this document will be used to assign specimen permissions for each specimen into the Entrusted Keyholder's Specimen Database.

c. eCRF Documentation for Future Biomedical Research Specimens

Documentation of both consent and acquisition of Future Biomedical Research specimens will be captured in the electronic Case Report Forms (eCRFs). Reconciliation of both forms will be performed to assure that only appropriately-consented specimens are used for this sub-study's research purposes. Any specimens for which such an informed consent cannot be verified will be destroyed.

d. Future Biomedical Research Specimen Collections

Blood specimens for DNA or RNA isolation will usually be obtained at a time when the subject is having blood drawn for other study purposes. Specimens like tissue and bone marrow will usually be obtained at a time when the subject is having such a procedure for clinical purposes.

Specimens will be collected and sent to the laboratory designated for the trial where they will be processed (e.g., DNA or RNA extraction, etc) following the Merck approved policies and procedures for specimen handling and preparation.

6.6.4 Confidential Subject Information for Future Biomedical Research

In order to optimize the research that can be conducted with Future Biomedical Research specimens, it is critical to link subject' clinical information with future test results. In fact little or no research can be conducted without connecting the clinical study data to the specimen. The clinical data allow specific analyses to be conducted. Knowing subject characteristics like gender, age, medical history and treatment outcomes are critical to understanding clinical context of analytical results.

To maintain privacy of information collected from specimens obtained for Future Biomedical Research, Merck has developed secure policies and procedures. All specimens will be de-identified as described below.

At the clinical site, unique codes will be placed on the Future Biomedical Research specimens for transfer to the storage facility. This first code is a random number which does not contain any personally identifying information embedded within it. The link (or key) between subject identifiers and this first unique code will be held at the study site. No personal identifiers will appear on the specimen tube.

This first code will be replaced with a second code at a Merck designated storage/lab facility. The second code is linked to the first code via a second key. The specimen is now double coded. Specimens with the second code are sometimes referred to as de-identified specimens. The use of the second code provides additional confidentiality and privacy protection for subjects over the use of a single code. Access to both keys would be needed to link any data or specimens back to the subject's identification.

The second code is stored separately from the first code and all associated personal specimen identifiers. A secure link, the second key, will be utilized to match the second code to the first code to allow clinical information collected during the course of the study to be associated with the specimen. This second key will be transferred under secure procedures by the Merck designated facility to an Entrusted Keyholder at Merck. The second code will be logged into the primary biorepository database at Merck and, in this database, this identifier will not have identifying demographic data or identifying clinical information (i.e., race, sex, age, diagnosis, lab values) associated with it. The specimen will be stored in a designated biorepository site with secure policies and procedures for specimen storage and usage.

The second key can be utilized to reconstruct the link between the results of future biomedical research and the clinical information, at the time of analysis. This linkage would not be possible for the scientist conducting the analysis, but can only be done by the Merck Entrusted Keyholder under strict security policies and procedures. The Merck Entrusted Keyholder will link the information and then issue a de-identified data set for analysis. The only other circumstance by which future biomedical research data would be directly linked to the full clinical data set would be those situations mandated by health authorities (e.g., EMEA, FDA), whereby this information would be directly transferred to the health authority.

6.6.5 Biorepository Specimen Usage

Specimens obtained for the Merck Biorepository will be used for analyses using good scientific practices. However, exploratory analyses will not be conducted under the highly validated conditions usually associated with regulatory approval of diagnostics. The scope of research performed on these specimens is limited to the investigation of the variability in biomarkers that may correlate with a clinical phenotype in subjects.

Analyses utilizing the Future Biomedical Research specimens may be performed by Merck, or an additional third party (e.g., a university investigator) designated by Merck. The investigator conducting the analysis will be provided with double coded specimens. Re-association of analysis results with corresponding clinical data will only be conducted by the Merck Entrusted Keyholder. Any contracted third party analyses will conform to the specific scope of analysis outlined in this sub-study. Future Biomedical Research specimens remaining with the third party after the specific analysis is performed will be returned to the sponsor or destroyed and documentation of destruction will be reported to Merck.

6.6.6 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 study. If medical records for the main study are still available, the investigator will contact MERCK using the designated mailbox (clinical.specimen.management@merck.com) and a form will be provided by MERCK 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 MERCK to the investigator confirming the destruction. It is the responsibility of the investigator to inform the patient 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 study data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main study are no longer available (e.g., if the investigator is no longer required by regulatory agencies to retain the main study records) or the specimens have been completely anonymized, there will no longer be a link between the patient’s personal information and their specimens. In this situation, the request for specimen destruction can not be processed.

6.6.7 Retention of Specimens

Future Biomedical Research specimens will be stored in the biorepository for potential analysis for up to 20 years from acquisition. Specimens may be stored for longer if a regulatory or governmental agency has active questions that are being answered. In this special circumstance, specimens will be stored until these questions have been adequately addressed.

Specimens from the site will be shipped to a central laboratory and then shipped to the Merck designated biorepository. The specimens will be stored under strict supervision in a limited access facility which operates to assure the integrity of the specimens. Specimens will be destroyed according to Merck policies and procedures and this destruction will be documented in the biorepository database.

6.6.8 Data Security

Separate databases for specimen information and for results from the Future Biomedical Research sub-study will be maintained by Merck. This is done to separate the future exploratory test results (which include genetic data) from the clinical trial database thereby maintaining a separation of subject number and these results. The separate databases are accessible only to the authorized sponsor and the designated study administrator research personnel and/or collaborators. Database user authentication is highly secure, and is accomplished using network security policies and practices based in international standards (e.g., ISO17799) to protect against unauthorized access. The Merck Entrusted Keyholder maintains control over access to all specimen data. These data are collected for future biomedical research purposes only as specified in this sub-study will not be used for any other purpose.

6.6.9 Reporting of Future Biomedical Research Data to Subjects

There is no definitive requirement in either authoritative ethical guidelines or in relevant laws/regulations globally that research results have to be, in all circumstances, returned to study participant. Some guidelines advocate a proactive return of data in certain instances. No information obtained from exploratory laboratory studies will be reported to the subject or family, and this information will not be entered into the clinical database maintained by Merck on subjects. Principle reasons not to inform or return results to the subject include: lack of relevance to subject health, limitations of predictive capability, concerns of misinterpretation, and absence of good clinical practices standards in exploratory research typically used for diagnostic testing.

If any exploratory results are definitively associated with clinical significance for subjects while the clinical trial is still ongoing, investigators will be contacted with information as to how to offer clinical diagnostic testing (paid for by Merck) to subjects enrolled and will be advised that counseling should be made available for all who choose to participate in this diagnostic testing.

If any exploratory results are definitively associated with clinical significance after completion of a clinical trial, Merck will publish the results without revealing specific subject information, inform all sites who participated in the Merck clinical trial, and post anonymized results on our website or other accredited website(s) that allow for public access (e.g., Disease societies who have primary interest in the results) in order that physicians and patients may pursue clinical diagnostic testing if they wish to do so.

6.6.10 Gender, Ethnicity, and Minorities

Although many diagnoses differ in terms of frequency by ethnic population and gender, every effort will be made to recruit all subjects diagnosed and treated on Merck clinical trials for future biomedical research. When studies with specimens are conducted and subjects identified to serve as controls, every effort will be made to group specimens from subjects and controls to represent the ethnic and gender population representative of the disease under current investigation.

6.6.11 Risks Versus Benefits of Future Biomedical Research

For future biomedical research, risks to the subject have been minimized. Risks include those associated with venipuncture to obtain the whole blood specimen. This specimen will be obtained at the time of routine blood specimens drawn in the main study.

Merck has developed strict security, policies and procedures to address subject data privacy concerns. Data privacy risks are largely limited to rare situations involving possible breach of confidentiality. In this highly unlikely situation there is risk that the information, like all medical information, may be misused.

It is necessary for subject-related data (i.e., ethnicity, diagnosis, drug therapy and dosage, age, toxicities, etc) to be reassociated to double coded specimens at the time of data analysis. These subject data will be kept in a separate, secure Merck database, and all specimens will be stripped of subject identifiers. No information concerning results obtained from future biomedical research will be entered into clinical records, nor will it be released to outside persons or agencies, in any way that could be tied to an individual subject.

6.6.12 Self-Reported Ethnicity

Subjects who participate in future biomedical research will be asked to provide self-reported ethnicity. Subjects who do not wish to provide this data may still participate in future biomedical research.

6.6.13 Questions

Any questions related to the future biomedical research should be e-mailed directly to clinical.specimen.management@merck.com.

7. ATTACHMENTS

Merck Code of Conduct for Clinical Trials

Understanding the Intent, Scope and Public Health Benefits of Exploratory Biomarker Research: A Guide for IRBs/IECs and Investigational Site Staff.

Merck*
Code of Conduct for Clinical Trials

I. Introduction

A. Purpose

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

B. Scope

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

II. Scientific Issues

A. Trial Conduct

1. Trial Design

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

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

2. Site Selection

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

3. Site Monitoring/Scientific Integrity

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

B. Publication and Authorship

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

Merck's policy on authorship is consistent with the requirements outlined in the ICH-Good Clinical Practice guidelines. In summary, authorship should reflect significant contribution to the design and conduct of the trial,

performance or interpretation of the analysis, and/or writing of the manuscript. All named authors must be able to defend the trial results and conclusions. Merck funding of a trial will be acknowledged in publications.

III. Subject Protection

A. IRB/ERC review

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

B. Safety

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

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

C. Confidentiality

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

D. Genomic Research

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

IV. Financial Considerations

A. Payments to Investigators

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

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

B. Clinical Research Funding

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

C. Funding for Travel and Other Requests

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

V. Investigator Commitment

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

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