Official Protocol Title:	Phase Ib Study of MK-3475 in Subjects with Advanced Melanoma
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TITLE:

Phase Ib Study of MK-3475 in Subjects with Advanced Melanoma

EudraCT NUMBER: Not Applicable

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SUMMARY OF CHANGES

PRIMARY REASON(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
1.0	TRIAL SUMMARY	After marketing approval of MK-3475, "clinical trial" will be replaced with "post-marketing clinical trial" and this study will be continued. Between the marketing approval of MK-3475 and 1) the delivery of marketed product of MK-3475 in each site, or 2) 6 months from marketing approval, whichever occurs first, the subjects can receive treatment of MK-3475 as post-marketing clinical trial drug.	1) This amendment makes continuing patients use MK-3475 on this protocol between the approval and the availability of marketed product of MK-3475 2) Due to the requirement of Japanese regulation, after marketing approval of MK-3475, "clinical trial" will be replaced with "post-marketing clinical trial ". 3) Patients can use study drug MK-3475 until the availability of marketed product of MK-3475 or 6 months from marketing approval, whichever occurs first.
2.1	Trial Design		
5.8	Subject Withdrawal/Discontinuation Criteria	"The delivery of marketed product of MK-3475 in each site" and "6 months from marketing approval" is added to the criteria of discontinuation from the treatment of MK-3475.	
9.1	Investigational Product	After the time of the marketing approval of MK-3475, "clinical trial drug" of MK-3475 will be replaced with "post-marketing clinical trial drug". Until the delivery of marketed product of MK-3475 in each site, the subjects can receive treatment of MK-3475 as post-marketing clinical trial drug	

1.0	TRIAL SUMMARY	"1) the marketing approval of MK-3475, 2) the completion of safety follow-up or 3) the time when a possibility of entry to second course is lost, whichever occurs last" is added into the criteria of discontinuation of this study.	Study end is 1) the marketing approval of MK-3475, 2) the completion of safety follow-up or 3) the time when a possibility of entry to second course is lost, whichever occurs last. More data becomes to be not required.
2.1	Trial Design		
5.8	Subject Withdrawal/Discontinuation Criteria		
1.0	TRIAL SUMMARY	The treatment of marketed product of MK-3475 is included to non-study cancer treatment	If patients start marketed product of MK-3475, safety follow-up for 30 days from the last dose of study drug MK-3475 should be required.
2.1	Trial Design		
2.1	Trial Design	Good Post-marketing Study Practice (GPSP) is added and this study is to be conducted in conformance with GPSP	In Japan, by law, filling of re-examination is required, based on information after approval. Post-marketing clinical trial is specified in GPSP and post-marketing clinical trial must obey GPSP.
10.3	Compliance with Law, Audit and Debarment		
10.5	Quality Management System		
13.2	Investigator		

ADDITIONAL CHANGE(S) FOR THIS AMENDMENT:

Section Number-(s)	Section Title-(s)	Description of Change-(s)	Rationale
5.2.1.2	Dose Modification (Escalation/Titration/Other)	Table 3 Dose Modification Guideline is updated. Instruction for Dose Modification is modified	Clarification and consistency in alignment with program level MK-3475 ECI guidance
5.6.1	Supportive Care Guidelines	Table 5 Recommended Approach to Handling Pneumonitis and Table 6 General Approach to Handling irAEs are deleted. Instruction for Supportive Care Guidelines is modified	
7.2	Assessing and Recording Adverse Events	Revised wording to provide further clarification on adverse event collection.	Clarification and consistency in alignment with program level MK-3475
4.2.1	Rationale for the Trial and Selected Subject Population	timing (at the start of this study) is added when newly therapies such as ipilimumab have not been approved yet in Japan	Therapies such as ipilimumab have been approved already in Japan now.

1.0 TRIAL SUMMARY

Abbreviated Title	Phase Ib Study of MK-3475 in Subjects with Advanced Melanoma
Trial Phase	Ib
Clinical Indication	The treatment of subjects with locally advanced or metastatic melanoma
Trial Type	Interventional
Type of control	No treatment control
Route of administration	Intravenous
Trial Blinding	Unblinded Open-label
Treatment Groups	MK-3475 2 mg/kg every 3 weeks (Q3W)
Number of trial subjects	Approximately 35 subjects will be enrolled.
Estimated duration of trial	The sponsor estimates that the trial will require approximately 10 months from the time the first subject signs the informed consent until the last subject's last visit.
Duration of Participation	Each subject will participate in the trial from the time the subject signs the Informed Consent Form (ICF) through the final protocol-specified contact. After a screening phase up to 4 weeks, eligible subjects will receive treatment on Day 1 of each 3-week dosing cycle. Treatment with MK-3475 will continue until the subject meets the discontinuation criteria such as 24 months of therapy completion, documented disease progression (per modified RECIST 1.1), or unacceptable toxicity, etc. Subjects who meet criteria for temporary discontinuation of study therapy after complete response (CR) may consider stopping trial treatment. These subjects may be eligible for re-treatment after experiencing disease progression at the discretion of the investigator if they meet the criteria for re-treatment for up to one year; this will be designated the Second Course Phase. After the end of treatment, each subject will be followed for a minimum of 30 days for adverse event monitoring (serious adverse events will be collected for up to 90 days after the end of treatment). Subjects who discontinue for reasons other than disease progression will have post-treatment follow-up for disease status until initiating a non-study cancer treatment (including the treatment of marketed product of MK-3475), disease progression, withdrawing consent, death, or the end of the study. All subjects will be followed by telephone for overall survival until death, withdrawal of consent, or the end of the study.

After marketing approval of MK-3475 for melanoma, "clinical trial" will be replaced with "post-marketing clinical trial" and this study will be continued. Between the marketing approval of MK-3475 for melanoma and 1) the delivery of marketed product of MK-3475 in each site, or 2) 6 months from marketing approval for melanoma, whichever occurs first, the subjects can receive treatment of MK-3475 as post-marketing clinical trial drug.

The end of the study of each subject is 1) the marketing approval of MK-3475 for melanoma, 2) the completion of safety follow-up or 3) the time when a possibility of entry to second course is lost, whichever occurs last.

2.0 TRIAL DESIGN

2.1 Trial Design

This is an open-label, non-randomized, multi-center Phase Ib study of MK-3475 in subjects with advanced melanoma to be conducted in conformance with Good Clinical Practices (GCP) and Good Post-marketing Study Practice (GPSP). Approximately 35 subjects will be enrolled in this trial to examine the safety and efficacy of the 2 mg/kg dose of MK-3475 administered every 3 weeks. The primary objectives of the trial are to determine the safety, tolerability, and overall response rate (ORR) per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) in subjects with advanced cutaneous melanoma. The secondary objectives include the duration of response (DOR), progression-free survival (PFS) per RECIST 1.1, and the ORR, DOR, and PFS per immune-related response criteria (irRC), and overall survival (OS) in subjects with advanced cutaneous melanoma. As the exploratory objectives, the efficacy (ORR, DOR, and PFS) per RECIST 1.1 and irRC and OS in subjects with advanced mucosal melanoma, the pharmacokinetic (PK) properties of MK-3475, the presence of anti-MK-3475 antibodies, pulmonary radiographic changes and its features, and the relationship between candidate biomarkers (including PD-L1 expression) and anti-tumor activity of MK-3475 will also be evaluated. Subjects will be evaluated every 6 weeks starting at 12 weeks through 48 weeks, and after 48 weeks, every 12 weeks with radiographic imaging to assess response to treatment. Tumor response will be assessed using RECIST 1.1 and irRC by the central independent radiology review. RECIST 1.1 will be used by the local site to determine eligibility and modified RECIST 1.1 will be used to make treatment decisions (refer to Section 4.2.3.2). Adverse events will be monitored throughout the trial and graded in severity according to the guidelines outlined in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

Treatment with MK-3475 will continue unless the subject meets the discontinuation criteria such as disease progression (evaluated by modified RECIST 1.1), unacceptable toxicity, or completion of 24 months of treatment with MK-3475 (refer to Section 5.8 for further details). Subjects who attain an investigator-determined confirmed CR may consider stopping trial treatment after receiving at least 24 weeks of treatment (Treatment Phase). Subjects who discontinue after at least 24 months of therapy for reasons other than disease progression or intolerability or who discontinue after attaining a CR may be eligible for up to one year of retreatment (Second Course Phase) after they have experienced radiographic disease progression. The decision to retreat will be at the discretion of the investigator only if no cancer treatment (including the treatment of marketed product of MK-3475) was administered since the last dose of MK-3475, the subject still meets the safety parameters listed in the Inclusion/Exclusion criteria and the trial remains open (refer to Section 7.1.5.2.1 for further details). After the end of treatment in Treatment Phase and Second Course phase, each subject will be followed for 30 days for adverse event monitoring (serious adverse events will be collected for 90 days after the end of treatment). Subjects who discontinue treatment for reasons other than disease progression will have post-treatment follow-up for disease status until initiating a non-study cancer treatment, disease progression, withdrawing consent, death, or the end of the study, whichever occurs first. Response and progression in the Second Course Phase will not count towards the ORR and PFS of the efficacy endpoint in

this trial. All subjects will be followed by telephone contact for overall survival until death, withdrawal of consent or the end of the study, whichever comes first. Clinical data may temporarily be locked to assess the efficacy endpoint, ORR per RECIST 1.1 for advanced melanoma when once all of the enrolled subject has either progression disease or has had an imaging 24 weeks after treatment initiation, whichever occurs first.

Participation in this trial will require submitting an archival tissue sample or newly obtained biopsy of a tumor lesion not previously irradiated for PD-L1 expression evaluation. This specimen will be evaluated at a central laboratory for expression status of PD-L1 by immunohistochemistry (IHC). Both PD-L1 positive and negative subjects will be enrolled in this trial, and the clinical activity in both subsets will be evaluated as a pre-defined subgroup analysis.

After marketing approval of MK-3475 for melanoma, “clinical trial” will be replaced with “post-marketing clinical trial” and this study will be continued. Between the marketing approval of MK-3475 for melanoma and 1) the delivery of marketed product of MK-3475 in each site, or 2) 6 months from marketing approval for melanoma, whichever occurs first, the subjects can receive treatment of MK-3475 as post-marketing clinical trial drug.

The end of the study of each subject is 1) the marketing approval of MK-3475 for melanoma, 2) the completion of safety follow-up or 3) the time when a possibility of entry to second course is lost, whichever occurs last.

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

2.2 Trial Diagram

The trial design is depicted in Figure 1 below.

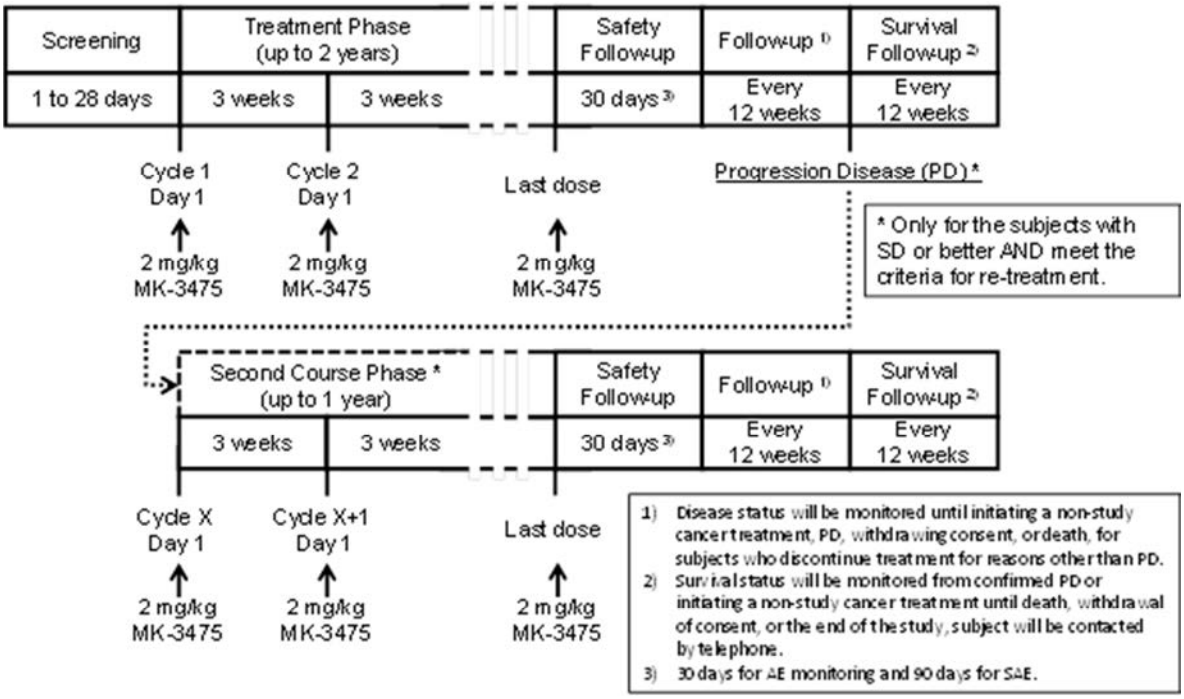


Figure 1 Trial Design Diagram

3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

3.1 Primary Objective(s) & Hypothesis(es)

1) **Objective:** To determine the safety and tolerability of the 2 mg/kg Q3W dose of MK-3475 in subjects with advanced melanoma.

2) **Objective:** To evaluate anti-tumor activity of the 2 mg/kg Q3W dose of MK-3475 in subjects with advanced cutaneous melanoma based on RECIST 1.1 assessed by the central independent radiology review.

   Hypotheses: Intravenous administration of single agent MK-3475 to subjects with advanced cutaneous melanoma will result in a clinically meaningful overall response rate (ORR) based on RECIST 1.1.

3.2 Secondary Objective(s) & Hypothesis(es)

1) **Objective**: To evaluate the duration of response (DOR) and progression-free survival (PFS) per RECIST 1.1 assessed by the central independent radiology review in subjects with advanced cutaneous melanoma receiving MK-3475.

2) **Objective**: To evaluate the ORR, DOR, and PFS per irRC assessed by the central independent radiology review in subjects with advanced cutaneous melanoma receiving MK-3475.

3) **Objective**: To evaluate the overall survival (OS) in subjects with advanced cutaneous melanoma receiving MK-3475.

3.3 Exploratory Objectives

1) **Objective**: To evaluate the efficacy (ORR, DOR, and PFS) per RECIST 1.1 and irRC assessed by the central independent radiology review and OS in subjects with advanced mucosal melanoma receiving MK-3475.

2) **Objective:** To explore the PK profile of MK-3475 in the advanced melanoma population.

3) **Objective:** To evaluate the presence of anti-MK-3475 antibodies.

4) **Objective:** To evaluate the pulmonary radiographic changes and its features for a diagnosis of MK-3475-induced pneumonitis.

5) **Objective:** To investigate the correlation between candidate biomarkers (including PD-L1 expression) and anti-tumor activity of MK-3475 in subjects with advanced melanoma.

4.0 BACKGROUND & RATIONALE

4.1 Background

4.1.1 Pharmaceutical and Therapeutic Background

MK-3475 is a potent and highly selective humanized monoclonal antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between PD-1 (programmed cell death-1) and its ligands PD-L1 and PD-L2. This blockade enhances functional activity of the target lymphocytes to facilitate tumor regression and ultimately immune rejection.

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

Melanoma is a malignant tumor of melanocytes, which are the cells that create the pigment melanin and are derived from the neural crest. Although melanoma accounts for less than 5% of skin cancer cases; it is the most lethal form and accounts for over 75% of skin cancer deaths [8]. Internationally, approximately 160,000 new cases of melanoma are diagnosed per year, with over 70% of these diagnosed in Australia, Europe, or North America [9-10]. In Japan, approximately 1,300 new cases of melanoma were diagnosed and more than 600 people died of melanoma in 2012 [Globocan 2012, IARC]. The incidence of melanoma is increasing worldwide, with a growing fraction of subjects with advanced disease for which prognosis remains poor. The median survival for subjects with metastatic melanoma has been under 1 year. The 5-year survival rate of patients with visceral involvement is under 10% and the goal of treatment for this incurable condition is palliative with marginal survival benefit [11].

Recent data with anti-PD-1 antibodies, including nivolumab (BMS-936558, ONO-4538) and MK-3475, have validated PD-1 as an attractive target for clinical intervention and have provided proof of concept for anti-PD-1 mAbs in melanoma [12-14]. Nivolumab has an observed objective response rate of 28% in melanoma subjects who had not previously received ipilimumab (IPI) [13]; MK-3475 has shown a promising response rate of 41% in melanoma subjects. Specifically, a response rate of more than 40% was observed with MK-3475 in melanoma subjects who have not received prior IPI treatment [15]. This response rate is much higher than the 11-15% response rate observed in IPI registration trials. Importantly, responses have been of long duration and both MK-3475 and nivolumab are generally well tolerated. Median overall survival of nivolumab was 16.8 months, and 1- and 2-year survival rates were 62% and 43%, respectively [15-16]. The median overall survival rate in melanoma of MK-3475 PN001 was not reached for the entire study population nor for any of the individual dose schedules at the time of the analysis. For all patients and dose schedules the fraction of patients alive at one year was more than approximately 80% [see Investigators Brochure (IB)]. Drug related AEs were reported for 340 of 411 (83%) in PN001 (all melanoma patients: Parts B1+B2+D). The most common drug-related AEs in melanoma subjects, reported in at least 10% of patients, were: fatigue (36.0%), pruritus (23.8%), rash (19.7%), nausea (12.2%), diarrhea (16.3%), arthralgia (15.6%), and vitiligo

(10.7%) (unpublished internal data: as of 18-Oct-2013). Safety data from PN001 indicate that most AEs were typically grade 1-2 in severity and reversible and that MK-3475 has an acceptable safety profile for the treatment of advanced melanoma patients.

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

4.1.2 Ongoing Clinical Trials

MK-3475 is being studied for various oncology indications including melanoma, non-small cell lung cancer, head and neck cancer, triple negative breast cancer, gastric cancer, bladder cancer, hematologic malignancies and other solid tumors. The overseas clinical development program in melanoma is ongoing and includes PN001, an open-label Phase I study evaluating the safety and efficacy of MK-3475; and two ongoing, randomized studies with active comparators (PN002/PN006). For trial details please refer to the IB.

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

As described in 4.1.1 Pharmaceutical and Therapeutic Background, MK-3475 has shown to be very well-tolerated and lead to objective response rates in melanoma subjects > 40% [15], and hence melanoma is considered to be one of the promising indications of potential tumors. Also, non-clinical and clinical data obtained so far supports clinical development of MK-3475 in Japan.

Treatment options for metastatic melanoma have been limited to chemotherapeutic agents such as dacarbazine and high-dose interleukin-2 immunotherapy. Outside Japan, there has been steady progress in the development of targeted therapy and immunotherapy for metastatic melanoma. BRAF inhibitors (vemurafenib and dabrafenib), anti-CTLA4 mAb (IPI), and MEK inhibitor (trametinib) were approved for treatment of metastatic melanoma in the past few years; however at the start of this study, these newly therapies have not been approved yet in Japan. Available treatment options for Japanese patients are currently limited to cytotoxic chemotherapies, which have very limited activity even in the first-line setting. Thus, the outcome of patients with metastatic melanoma still remains dismal and the development of new effective therapy is still needed.

This is a multi-center, open-label, Phase Ib trial of MK-3475 in subjects with advanced melanoma. Subjects with 0-2 prior lines of therapy will be enrolled in this trial. All subjects will be required to submit a tumor tissue sample for PD-L1 expression evaluation as a pre-defined subgroup analysis.

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

4.2.2 Rationale for Dose Selection/Regimen

The dosing regimen of MK-3475 in this study was determined based on the results from the overseas ongoing phase I study (PN001, refer to IB). PK data analysis of MK-3475 administered Q3W showed slow systemic clearance, limited volume of distribution, and a long half-life (13-21 days). Pharmacodynamic data (IL-2 release assay) suggested that peripheral target engagement is durable (>21 days). This early PK and pharmacodynamic data provides scientific rationale for testing Q3W dosing schedule. Also, preliminary preclinical data in syngeneic mouse tumor models suggests that sustained inhibition of PD-1 is important for maintaining anti-tumor activity (unpublished internal data). Thus, MK-3475 will be given until disease progression, unacceptable toxicity, or completion of 24 months of treatment with MK-3475 in the trial. The only exception is those patients who experience a confirmed CR; these patients may discontinue treatment with MK-3475 at the discretion of the investigator (see Section 5.8.1 for details).

A recent interim analysis from PN001 reported that, when evaluated in a randomized setting (in Cohorts B2 and D), the efficacy of MK-3475 given Q3W is comparable between 2 mg/kg and 10 mg/kg doses, indicating no improvement in efficacy with a 5-fold higher dose of MK-3475 beyond the 2 mg/kg dose (as determined by ORR, PFS, and OS endpoints). Similarly, the safety and AE profile of MK-3475 also appear similar between the 2 mg/kg Q3W and 10 mg/kg Q3W doses. Finally, PK analysis indicates a flat exposure-efficacy relationship beyond the 2 mg/kg dose. Taken together, these analyses indicate that the 2 mg/kg dose is associated with optimal efficacy and safety when MK-3475 is administered on a Q3W schedule for the patients with advanced melanoma (unpublished internal data; an ongoing study will compare efficacy and safety of 10 mg/kg Q2W vs 10 mg/kg Q3W in a randomized manner).

4.2.3 Rationale for Endpoints

4.2.3.1 Safety Endpoints

The primary safety objective of this study is to characterize the safety and tolerability of MK-3475 in subjects with advanced melanoma. In addition to general laboratory tests, immune laboratory test will be evaluated considering the mode of action of MK-3475. The primary safety analysis will be based on subjects who experienced toxicities as defined by CTCAE criteria. Safety will be assessed by quantifying the toxicities and grades experienced by subjects who have received MK-3475, including serious adverse events (SAEs) and events of clinical interest (ECIs).

Safety will be assessed by reported adverse experiences using CTCAE, Version 4.0. The attribution to drug, time-of-onset, duration of the event, its resolution, and any concomitant medications administered will be recorded. AEs will be analyzed including but not limited to all AEs, SAEs, fatal AEs, and laboratory changes. Furthermore, specific immune-related adverse events (irAEs) will be collected and designated as immune-related events of clinical interest (ECIs) as described in Section 7.2.3.2. Since pneumonitis has been previously reported in clinical studies of anti-PD-1 antibodies including MK-3475, pulmonary radiographic changes and its features will be evaluated by investigators and an independent radiologist from a potential risk of pneumonitis.

4.2.3.2 Efficacy Endpoints

The primary efficacy objective of this study is to evaluate ORR per RECIST 1.1 in subjects with advanced cutaneous melanoma. The secondary objectives are to evaluate DOR and PFS per RECIST 1.1, ORR, DOR, and PFS per irRC, and OS in subjects with advanced cutaneous melanoma. In this study, the efficay in subjects with advanced mucosal melanoma will also be evaluated as an exploratory objective. Having considered the rarity, unique biology, and poor prognosis of mucosal melanoma, the proportion of subjects with mucosal melanoma in this study is limited up to 20% of the total subjects. Response rates per RECIST 1.1 [17] and irRC [18] will be evaluated by the central independent radiology review. RECIST 1.1 will be used by the local site to determine eligibility and modified RECIST 1.1 will be used to make treatment decisions.

RECIST 1.1 will be adapted to account for the unique tumor response characteristics seen with treatment of MK-3475. Immunotherapeutic agents such as MK-3475 may produce antitumor effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents, and can manifest a clinical response after an initial increase in tumor burden or even the appearance of new lesions. Standard RECIST may not provide an accurate response assessment of immunotherapeutic agents such as MK-3475. Therefore, modified RECIST 1.1 will be used with the adaptations (refer to Section 7.1.3.4), in which a confirmation assessment of disease progression must be obtained at least 4 weeks after the initial disease assessment indicating progressive disease.

The irRC are a published set of guidelines proposed for immunotherapies in solid tumors. Inclusion of this method is based on the observation that some patients with melanoma may have a transient increase in measured tumor size or small new lesions on CT scans (due to infiltration of inflammatory cells) in the first few months after start of immunotherapy, with subsequent reduction in tumor size (due to immune-mediated tumor cell kill). Immune-based response criteria differ predominantly from RECIST 1.1 by measurement of lesions using two dimensions rather than one, as well as inclusion of new lesions into the overall tumor burden calculation, rather than having new lesions automatically define progression (refer to Section 7.1.3.4).

4.2.3.3 Pharmacokinetic/Immunogenicity Endpoints

Serum samples will be obtained to measure pharmacokinetics of MK-3475. In addition, an exploratory investigation on the formation of anti-MK-3475 antibody and its effect on the pharmacokinetics of MK-3475 will also be evaluated for interpretation of immunogenicity results considering MK-3475 is a humanized monoclonal anti-PD-1 antibody. Subsequently, the concentration-time data to be obtained from MK-3475 serum assay will be diverted to a population PK analysis (or non-compartment analysis). The sampling time points for MK-3475 pharmacokinetics and anti-MK-3475 antibody have been determined taking the long half-life (two to three weeks) of MK-3475 into account. The timepoints for PK blood sampling are described in Section 6 – Trial Flow Chart.

4.2.3.4 Planned Exploratory Biomarker Research

Biomarker research to identify factors important for MK-3475 monotherapy may also be pursued. For example, tumor and blood samples from this study may undergo proteomic, genomic and transcriptional analyses (both DNA and RNA analyses). PD-L1 expression by IHC will be evaluated retrospectively and the clinical activity in PD-L1 positive and negative subjects will be evaluated. Additional research may evaluate factors important for predicting responsiveness or resistance to MK-3475 therapy and other immunologic targets.

Assays may include but are not be limited to:

Transcriptional Analyses

Messenger RNA (mRNA) expression profiling in archival material will be completed to assess expression of approximately 600 genes and attempt to define a gene set critical for clinical response to MK-3475. The hypothesis to be tested is that MK-3475 responders will exhibit a “stalled CTL” response within the tumor reflected in the physical proximity between PD-1 and PD-L1 expression and the presence of an aborted (e.g., weak but discernible) interferon-gamma transcriptional program will be detectable by profiling analyses. Global profiling will also be pursued. Expression of individual genes related to the immune system may also be evaluated such as immune signatures and critical cytokines (e.g., IL-10).

Gene Analyses

New data are emerging that suggest we can define certain tumor types as being ‘hypermutated’. There is a potential that this hypermutated state may correlate with response to MK-3475 therapy, and/or that the converse, ‘hypomutated’ state may correlate with nonresponse.

In addition, DNA isolated from blood or tumor tissue will be analyzed in order to identify genetic alterations and to evaluate specific genetic alterations that may correlate with clinical response to MK-3475. These and other additional biomarker or genomic research to identify factors important for MK-3475 therapy (for example, HLA genotype) may also be pursued.

4.2.3.5 Future Biomedical Research

The Sponsor will conduct Future Biomedical Research on blood and tumor tissue specimens routinely and specifically 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.

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 pharmacogenetic (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/vaccines, and/or to ensure that subjects receive the correct dose of the correct drug/vaccine at the correct time. The details of this Future Biomedical Research sub-trial are presented in Section 12.2 - 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 Section 12.3.

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

Male/Female subjects with advanced melanoma of at least 20 years will be enrolled in this trial.

5.1.2 Subject Inclusion Criteria

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

1. Be willing and able to provide written informed consent for the trial. The subject may also provide consent for Future Biomedical Research. However, the subject may participate in the main trial without participating in Future Biomedical Research.

2. Be ≥ 20 years of age on day of signing informed consent.

3. Have histologically confirmed diagnosis of locally advanced (unresectable Stage III) or metastatic (Stage IV) melanoma not amenable to local therapy.

    - Subject may not have a diagnosis of uveal or ocular melanoma.
    - Subject who have mucosal melanoma are eligible.

      NOTE: the proportion of subjects with mucosal melanoma will not exceed 20% of the total subjects (limited up to 7 subjects).

    - Subject who have received 0-2 prior lines of therapy (excluding adjuvant or neoadjuvant therapy) for melanoma.
    - LDH ≤ local ULN

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

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

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

5. Have a performance status of 0 or 1 on the ECOG Performance Scale.

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

7. Demonstrate adequate organ function as defined in Table 1, all screening labs should be performed within 10 days of treatment initiation.

Table 1 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥ 1,500 /mcL (without supportive care)
Platelets	≥ 100,000 / mcL
Hemoglobin	≥9 g/dL or ≥5.6 mmol/L (without transfusions)
Renal	
Serum creatinine **OR** Measured or calculated creatinine clearance (CrCl) [a] (GFR can also be used in place of creatinine or CrCl)	≤ 1.5 X upper limit of normal (ULN) **OR** ≥50 mL/min for subjects with creatinine levels > 1.5 X institutional ULN
Hepatic	
Serum total bilirubin	≤ 1.5 X ULN (or < 3x ULN in subjects with Gilbert's syndrome) **OR** direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 X ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 X ULN **OR** ≤ 5 X ULN for subjects with liver metastases
Endocrine	
Thyroid stimulating hormone (TSH)	Within normal range
Coagulation	
Prothrombin Time (PT) / International Normalized Ratio (INR), activated Partial Thromboplastin Time (aPTT)	≤1.5 X ULN unless the subject is receiving anticoagulant therapy as long as PT or aPTT is within therapeutic range of intended use of anticoagulants
[a] Creatinine clearance should be calculated per institutional standard. If no local guideline is available, Creatinine Clearance should be calculated using the Cockcroft-Gault Method: CrCl = [(140-age) * weight (kg) * (0.85 for females only)] / (72 * serum creatinine)	

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

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

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

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

10. (Female subject of childbearing potential) Have a negative urine or serum pregnancy test within 72 hours prior to receiving the first dose of study medication. If the urine test is positive or borderline a serum pregnancy test will be required.

11. (Female subjects of childbearing potential) Be willing to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study medication (Refer to Section 5.7.2). The commonly used criteria for subjects of child bearing potential are those who have not been surgically sterilized or have not been free from menses for >1 year.

12. (Male subjects) Agree to use an adequate method of contraception starting with the first dose of study therapy through 120 days after the last dose of study therapy.

5.1.3 Subject Exclusion Criteria

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

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

2. Is currently participating or has participated in a study with an investigational compound or device within 30 days, or 5X half-life of the investigational compound, whichever is longer, of initial dosing on this study.

3. Has had chemotherapy, targeted small molecule therapy, radiotherapy, or biological cancer therapy (including monoclonal antibodies) within 4 weeks prior to the first dose of trial treatment, or who has not recovered (≤ Grade 1 or baseline) from adverse events due to a previously administered agent.

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

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

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

   Note: Exceptions include adequately treated Stage 1 or Stage 2 basal/squamous cell carcinoma of the skin, superficial bladder cancer, or cancer in situ which has undergone potentially curative therapy, or no evidence of that disease recurrence for 5 years since initiation of that therapy.

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

6. Has known active central nervous system (CNS) mets and/or carcinomatous meningitis.

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

7. Has an active autoimmune disease requiring systemic treatment within the past 3 months prior to first study drug administration, a documented history of clinically severe autoimmune disease, or a syndrome that requires systemic steroids or immunosuppressive agents.

   Note: Subjects with vitiligo, diabetes mellitus type I, or resolved childhood asthma/atopy would be an exception to this rule. Subjects that require intermittent use of bronchodilators or local steroid injections would not be excluded from the study. Subjects with hypothyroidism stable on hormone replacement or Sjorgen's syndrome will not be excluded from the study.

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

9. Has an active infection requiring intravenous systemic therapy.

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

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

12. Has history or evidence of active pneumonitis.

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

14. Has known history of active Hepatitis B (HBsAg reactive) or C (HCV RNA [qualitative] is detected).

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

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

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

18. Is or has an immediate family member (e.g., spouse, parent/legal guardian, sibling or child) who is investigational site or sponsor staff directly involved with this trial unless, prospective IRB approval (by chair or designee) is given allowing exception to this criterion for a specific subject.

5.2 Trial Treatment(s)

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

Table 2 Trial Treatment

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment	Use
MK-3475	2 mg/kg	Q3W	IV infusion	Day 1 of each cycle	Experimental
The MK-3475 dosing interval may be increased due to toxicity as described in Section 5.2.1.2.					

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

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

5.2.1 Dose Selection/Modification

5.2.1.1 Dose Selection (Preparation)

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

5.2.1.2 Dose Modification (Escalation/Titration/Other)

Adverse events (both non-serious and serious) associated with pembrolizumab exposure may represent an immunologic etiology. These adverse events may occur shortly after the first dose or several months after the last dose of treatment. Pembrolizumab must be withheld for drug-related toxicities and severe or life-threatening AEs as per Table 3 below. See Section 5.6 for supportive care guidelines, including use of corticosteroids.

Table 3 Dose Modification Guideline

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

Note: Permanently discontinue for any severe or Grade 3 (Grade 2 for pneumonitis) drug-related AE that recurs, or any life-threatening event.
[a] For patients with liver metastasis who begin treatment with Grade 2 AST or ALT, if AST or ALT increases by greater than or equal to 50% relative to baseline and lasts for at least 1 week then patients should be discontinued.
[b] If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose; Refer to Table 4 – Infusion Treatment Guidelines for further management details.
[c] Patients with intolerable or persistent Grade 2 drug-related AE may hold study medication at physician discretion. Permanently discontinue study drug for persistent Grade 2 adverse reactions for which treatment with study drug has been held, that do not recover to Grade 0-1 within 12 weeks of the last dose.

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

5.2.2 Timing of Dose Administration

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

All trial treatments will be administered on an outpatient basis. The specific time of trial treatment infusion (e.g., time of the week for first administration; time of the day for each administration) should take into consideration PK sampling time points and study visit procedures.

5.2.3 Trial Blinding/Masking

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

5.3 Randomization or Treatment Allocation

Subjects participating in this trial will be allocated by non-random assignment.

5.4 Stratification

No stratification based on age, sex or other characteristics will be used in this trial.

5.5 Concomitant Medications/Vaccinations (Allowed & Prohibited)

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for any medication or vaccination specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The investigator should discuss any questions regarding this with the Sponsor Clinical Director. The final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary physician. However, the decision to continue the subject on trial therapy or vaccination schedule requires the mutual agreement of the investigator, the Sponsor and the subject.

5.5.1 Allowed Concomitant Medications

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

All prior/concomitant medications received within 4 weeks before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered after 30 days after the last dose of trial treatment should be recorded for SAEs and ECIs as defined in Section 7.2.

5.5.2 Prohibited Concomitant Medications

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

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Investigational agents other than MK-3475
- Radiation therapy
    - Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed after consultation with Sponsor.
- Live vaccines within 4 weeks prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally inactivated flu vaccines and are allowed.
- Glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology.
    - Note: The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.

Subjects who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the trial. Subjects may receive other medications that the investigator deems to be medically necessary. Local surgery or radiation therapy (if indicated for palliative measure only after discussion with the SPONSOR) may be permitted beyond Week 24 tumor assessment.

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

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

5.6 Rescue Medications & Supportive Care

5.6.1 Supportive Care Guidelines

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

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

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

- **Pneumonitis**:
    - For **Grade 2 events**, treat with systemic corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
    - For **Grade 3-4 events**, immediately treat with intravenous steroids. Administer additional anti-inflammatory measures, as needed.
    - Add prophylactic antibiotics for opportunistic infections in the case of prolonged steroid administration.
- **Diarrhea/Colitis**:

  Subjects should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus).
    - All subjects who experience diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion. For Grade 2 or higher diarrhea, consider GI consultation and endoscopy to confirm or rule out colitis.

- For **Grade 2 diarrhea/colitis,** administer oral corticosteroids.
- For **Grade 3 or 4 diarrhea/colitis,** treat with intravenous steroids followed by high dose oral steroids.
- When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

- **Type 1 diabetes mellitus (if new onset, including diabetic ketoacidosis [DKA]) or ≥ Grade 3 Hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA)**
  - For **T1DM** or **Grade 3-4** Hyperglycemia
    - Insulin replacement therapy is recommended for Type I diabetes mellitus and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria.
    - Evaluate patients with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.
- **Hypophysitis**:
  - For **Grade 2** events, treat with corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
  - For **Grade 3-4** events, treat with an initial dose of IV corticosteroids followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
- **Hyperthyroidism or Hypothyroidism**:

  Thyroid disorders can occur at any time during treatment. Monitor patients for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders.
  - **Grade 2** hyperthyroidism events (and **Grade 2-4** hypothyroidism):
    - In hyperthyroidism, non-selective beta-blockers (e.g. propranolol) are suggested as initial therapy.
    - In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyroinine, is indicated per standard of care.

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

- **Hepatic**:
  - For **Grade 2** events, monitor liver function tests more frequently until returned to baseline values (consider weekly).
    - Treat with IV or oral corticosteroids
  - For **Grade 3-4** events, treat with intravenous corticosteroids for 24 to 48 hours.
  - When symptoms improve to Grade 1 or less, a steroid taper should be started and continued over no less than 4 weeks.

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

- **Management of Infusion Reactions**: Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion.

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

Table 4 Infusion Reaction Treatment Guidelines

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

5.7 Diet/Activity/Other Considerations

5.7.1 Diet

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

5.7.2 Contraception

MK-3475 may have adverse effects on a fetus in utero. Furthermore, it is not known if MK-3475 has transient adverse effects on the composition of sperm. Non-pregnant, non-breast-feeding women may be enrolled if they are willing to use 2 methods of birth control or are considered highly unlikely to conceive. Highly unlikely to conceive is defined as 1) surgically sterilized, or 2) postmenopausal (a woman who is ≥45 years of age and has not had menses for greater than 1 year will be considered postmenopausal), or 3) not heterosexually active for the duration of the study. The two birth control methods can be either two barrier methods or a barrier method plus a hormonal method to prevent pregnancy. Subjects should start using birth control from study Visit 1 throughout the study period up to 120 days after the last dose of study therapy.

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

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

5.7.3 Use in Pregnancy

If a subject inadvertently becomes pregnant while on treatment with MK-3475, the subject will immediately be removed from the study. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the SPONSOR without delay and within 24 hours if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The 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.

5.7.4 Use in Nursing Women

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

5.8 Subject Withdrawal/Discontinuation Criteria

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

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

- The subject or legal representative (such as a parent or legal guardian) withdraws consent.
- The marketing approval of MK-3475 for melanoma, the completion of all safety follow-up or the time when a possibility of entry to second course is lost (e.g. the time of decision by investigator or subject for no enter to second course, the start of a new anti-cancer therapy, the delivery of marketed product of MK-3475 in each site, 6 months from marketing approval), whichever occurs last

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

- Radiographic disease progression

  Note: A subject may be granted an exception to continue on treatment with confirmed radiographic progression if clinically stable or clinically improved, please see Section 7.1.3.4
- Unacceptable adverse experiences as described in Section 5.2.1.2
- Intercurrent illness that prevents further administration of treatment
- Completed 24 months of treatment with MK-3475

  Note: 24 months of study medication is calculated from the date of first dose. Subjects who stop MK-3475 after 24 months may be eligible for up to 1 year of additional study treatment if they progress after stopping study treatment provided they meet the requirements detailed in Section 7.1.5.2.1.
- Investigator's decision to withdraw the subject
- The subject has a confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements

- The subject is lost to follow-up
- Administrative reasons
- The delivery of marketed product of MK-3475 in each site
- 6 months from marketing approval for melanoma

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

5.8.1 Temporary Discontinuation of Study Therapy after CR

Discontinuation of treatment may be considered for subjects who have attained an investigator-determined confirmed CR per modified RECIST 1.1 that have been treated for at least 24 weeks with MK-3475 and had at least two treatments with MK-3475 beyond the date when the initial CR was declared. Subjects who then experience radiographic disease progression per modified RECIST 1.1 may be eligible for up to 1 year of additional treatment with MK-3475 at the discretion of the investigator if no cancer treatment was administered since the last dose of MK-3475, the subject meets the safety parameters listed in the Inclusion/Exclusion criteria, and the trial is open. Subjects will resume therapy at the same dose and schedule at the time of initial discontinuation. Additional details are provided in Section 7.1.5.2.1.

5.9 Subject Replacement Strategy

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

5.10 Beginning and End of the Trial

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

5.11 Clinical Criteria for Early Trial Termination

There are no pre-specified criteria for terminating the trial early.

6.0 TRIAL FLOW CHART

6.1 Treatment Phase

Treatment Cycle (Week) / Title:	Screening	Treatment Cycles (2 mg/kg Q3W) [1]								End of Treatment	Post-Treatment		
	(-4)	1 (0)	2 (3)	3 (6)	4 (9)	5 (12)	6 (15)	7 (18)	8 (21) and beyond	Discon	Safety Follow-up	Follow Up Visits [2]	Survival Follow-Up [3]
Scheduling Window (Days):	-28		±3	±3	±3	±3	±3	±3	±3	At time of Discon	30 days (±3) post discon	Every 12 weeks (±7) post discon	
Administrative Procedures													
Informed Consent [4]	X												
Informed Consent for Future Biomedical Research (Optional)	X												
Inclusion/Exclusion Criteria	X												
Subject Identification Card	X												
Demographics and Medical History	X												
Prior/Concomitant Medication Review [5]	X	X	X	X	X	X	X	X	X	X	X		
Trial Treatment Administration		X	X	X	X	X	X	X	X				
Post-study anticancer therapy status												X	X
Survival Status													X
Clinical Procedures/Assessments													
Review Adverse Events [6]	X----------												----------X
Full Physical Examination [7]	X					X			X				
Directed Physical Examination [7]		X	X	X	X		X	X		X			
Vital Signs, Height and Weight [8]	X	X	X	X	X	X	X	X	X	X			
12-Lead ECG [9]	X	X							X		X		
ECOG Performance Status	X	X	X	X	X	X	X	X	X	X	X	X	
Laboratory Procedures/Assessments: analysis performed by local laboratory													
Pregnancy Test (Urine or Serum β-HCG) [10]	X												
Coagulation Parameters [11], [12]	X												
Hematology and Chemistry [12]	X		X	X	X	X	X	X	X	X	X [13]		
Urinalysis [12]	X						X			X	X [13]		
FT3, FT4 and TSH [12]	X					X		X		X	X [13]		
KL-6, β-D glucan [14]	X												
Laboratory Procedures/Assessments: analysis performed by central laboratory													
Pharmacokinetics [15]		X	X		X				X		X		
Anti-MK-3475 Antibodies [15]		X	X		X				X		X		
Correlative Studies Blood Collection [16]		X [17]								X			
Blood for Future Biomedical Research (optional)		X [18]											
Efficacy Measurements													

Treatment Cycle (Week) / Title:	Screening	Treatment Cycles (2 mg/kg Q3W) [1]								End of Treatment	Post-Treatment		
	(-4)	1 (0)	2 (3)	3 (6)	4 (9)	5 (12)	6 (15)	7 (18)	8 (21) and beyond	Discon	Safety Follow-up	Follow Up Visits [2]	Survival Follow-Up [3]
Scheduling Window (Days):	-28		±3	±3	±3	±3	±3	±3	±3	At time of Discon	30 days (±3) post discon	Every 12 weeks (±7) post discon	
Tumor Imaging [19]	X					X		X				X	
Digital Photography (if applicable) [20]	X					X		X				X	
Tumor Tissue Collection [21]	X												
BRAF Testing [22]	X												

1) In general, assessments/procedures are to be performed on Day 1 and prior to the first dose of treatment for each cycle, and the window for each visit is ± 3 days unless otherwise specified. Treatment cycles are 3 weeks (Q3W); however the treatment cycle interval may be increased due to toxicity according to the dose modification guidelines provided in Section 5.2.1.2. If the interval is increased, all procedures except imaging should be performed based on the new dosing schedule.
2) In subjects who discontinue study therapy without documented disease progression, every effort should be made to continue monitoring their disease status by radiologic imagingx every 12 weeks (± 1 week) until (1) the start of new anti-cancer treatment, (2) documented disease progression, (3) death, or (4) the end of the study, whichever occurs first.
3) After the start of new anti-cancer treatment or documented disease progression, the subject should be contacted by telephone every 12 weeks to assess for survival status.
4) Written consent must be obtained prior to performing any protocol specific procedure. Results of a test performed prior to the subject signing consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame (e.g., within 4 weeks prior to the first dose of trial treatment). Screening number will be assigned when the study informed consent is signed.
5) Prior medications - Record all medications taken within 4 weeks of screening visit. Concomitant medications - Enter new medications started during the trial through the Safety Follow-up visit. Record all medications taken for SAE/ECI s as defined in Section 7.2.
6) Record all AEs occurring within 30 days after the last dose of trial treatment. Report all SAEs occurring within 90 days after the last dose of trial treatment or 30 days of the end of treatment if the subject initiates new anticancer therapy, whichever is earlier. Report all ECIs occurring up until 90 days after the last dose of trial treatment or the start of new anti-cancer treatment, whichever comes first. Afterwards, report only SAEs and ECIs that are related to trial treatment. Adverse experiences and laboratory safety measurements will be graded per NCI CTCAE version 4.0. All adverse experiences, whether gradable by CTCAE or not, will also be evaluated for seriousness.
7) Perform physical examinations at predose on the day of the study treatment visit. A full physical examination will be performed at screening and every 3 cycles after Cycle 5.
8) Vital signs to include temperature, pulse, respiratory rate, weight and blood pressure. If a patient's baseline weight does not fluctuate by more than 10%, this weight can be used to calculate dose. Height will be measured at screening only.
9) ECG should be performed within 30 minutes of the end of infusion after dosing for Cycle 1 and Cycle 8, and 30 day post-discontinuation.
10) For women of reproductive potential, a urine pregnancy test should be performed within 72 hours prior to first dose of trial treatment. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test performed by the local study site laboratory will be required. Pregnancy tests (serum and/or urine tests) should be repeated if required by local guidelines.
11) Coagulation factors (PT/INR and aPTT) should be tested as part of the screening procedures for all subjects. Any subject receiving anticoagulant therapy should have coagulation factors monitored closely throughout the trial.
12) Laboratory tests for screening are to be performed locally within 10 days prior to the first dose of trial treatment. After Cycle 1, lab samples can be collected up to 72 hours prior to the scheduled time point. Following Cycle 6, urinalysis should be performed every 6 cycles and FT3, FT4 and TSH should be performed every 2 cycles. See Section 7.1.3 for details regarding laboratory tests.
13) Unresolved abnormal labs that are drug related AEs should be followed until resolution. Labs do not need to be repeated after the end of treatment if labs are within normal range.
14) KL-6 and β–D glucan will be measured for pulmonary evaluation at screening (within 10 days prior to the first dose of study treatment) and thereafter if a subject develops suspected pneumonitis, an additional test may be performed at the descretion of the investigator.

15) Trough (pre-dose) and peak (post-dose) PK samples will be collected at Cycles 1 and 8. A trough sample only will be collected at Day 1 of Cycles 2, 4, 9, 13 and 17 (following Cycle 17, every 4 cycles), 30 days after discontinuation of study drug, and 12 weeks and 24 weeks after discontinuation of study drug (or until the subject starts new anti-neoplastic therapy). All trough samples should be drawn within 24 hours before infusion of MK-3475. All peak samples should be drawn within 30 minutes and between 72 to 168 hours (Day 4 to 8 of Cycles 1 and 8) after the end of the infusion. Anti-MK-3475 antibodies should be drawn with all pre-dose trough PK samples, the 30 day discontinuation draw and 12 weeks and 24 weeks after discontinuation of study drug (or until the subject starts new anti-neoplastic therapy). Procedures for sample collection are described in the Procedures Manual.
16) Blood for transcriptional analyses should be collected prior to Cycle 1, postdose at Day 4 to 8 of Cycle 1 (between 72 to 168 hours after the end of the infusion of Cycle 1 with PK sample), and again at treatment discontinuation. Blood for genetic analyses should be collected prior to Cycle 1.
17) The sample for genetic analysis should be collected unless there is a documented law or regulation or IRB/IEC ruling prohibiting a required collection for genetic analysis.
18) Informed consent for future biomedical research samples must be obtained before the DNA sample. DNA sample for analysis should be obtained predose, on Day 1 (or with the next scheduled blood draw) as the last sample drawn or at a later date as soon as the informed consent is obtained. Detailed instructions for the collection and management of specimens for FBR are provided in the Procedures Manual and Section 12.2.
19) The initial tumor imaging will be performed within 4 weeks prior to the first dose of trial treatment. Scans performed as part of routine clinical management are acceptable for use as the screening scan if they are of diagnostic quality and performed within 4 weeks prior to the first dose of trial treatment. On-study imaging should be performed every 6 weeks initially (± 1 week) starting at 12 weeks through 48 weeks, and after 48 weeks, imaging assessments should be performed every 12 weeks (i.e. Screening visit, Cycles 5, 7, 9, 11, 13, 15, 17 and then every 4 cycles [12 weeks]) or more frequently if clinically indicated. Imaging timing should follow calendar days and should not be adjusted for delays in cycle starts or extension of MK-3475 cycle frequencies. The same imaging technique should be used in a subject throughout the trial. Local reading (investigator assessment with site radiology reading) will be used to determine eligibility; Sponsor will collect radiological assessments for retrospective analysis by a central vendor. The processes for image collection and transmission to the central vendor are in the Investigator Imaging Operations Manual (IIOM). After the first documentation of progression (if the subject is clinically stable) or response per modified RECIST 1.1 used in this protocol, repeat imaging for confirmation is required. Confirmatory imaging may be performed as early as 4 weeks later; alternately, the scan performed at the next scheduled timepoint may be used as confirmation. CTs should include the chest, abdomen, and pelvis. A chest CT performed for tumor imaging will be used for pulmonary radiographic evaluation.
20) Qualitative digital photography should be performed at baseline and at time of scheduled tumor assessments for cutaneous lesions. Cutaneous lesions are not considered measurable for the purposes of this protocol, but may be considered to be non-target lesions for tumor assessments by investigators. Copies of digital photographs should also be submitted to the central imaging vendor.
21) Tumor tissue for biomarker analysis from an archival tissue sample or newly obtained biopsy (core or excisional: FNA/EBUS not adequate) of a tumor lesion not previously irradiated must be provided to the central vendor for characterization of PD-L1 status. These samples are not required to be obtained within 4 weeks of enrollment. Detailed instructions for tissue collection, processing and shipment are provided in the Procedures Manual. If the subject signs the Future Biomedical Research (FBR) consent, any leftover tissue that would ordinarily be discarded at the end of the study will be retained for FBR.
22) BRAF V600 mutation analysis should be performed locally by the sites or at the central lab during screening in subjects without documented BRAF status.

6.2 Second Course Phase (Retreatment ONLY)

Treatment Cycle (Week) / Title:	Treatment Cycles (2 mg/kg Q3W) [1]								End of Treatment	Post-Treatment		
	1 (0)	2 (3)	3 (6)	4 (9)	5 (12)	6 (15)	7 (18)	8 (21) and beyond	Discon	Safety Follow-up	Follow Up Visits [2]	Survival Follow-Up [3]
Scheduling Window (Days):		±3	±3	±3	±3	±3	±3	±3	At time of Discon	30 days (±3) post discon	Every 12 weeks (±7) post discon	
Administrative Procedures												
Eligibility Criteria (See Section 7.1.5.2.1)	X											
Concomitant Medication Review [4]	X	X	X	X	X	X	X	X	X	X		
Trial Treatment Administration	X	X	X	X	X	X	X	X				
Post-study anticancer therapy status											X	X
Survival Status												X
Clinical Procedures/Assessments												
Review Adverse Events [5]	X ---------- X											
Full Physical Examination [6]	X				X			X				
Directed Physical Examination [6]		X	X	X		X	X		X			
Vital Signs and Weight [7]	X	X	X	X	X	X	X	X	X			
12-Lead ECG [8]	X							X		X		
ECOG Performance Status	X	X	X	X	X	X	X	X	X	X	X	
Laboratory Procedures/Assessments: analysis performed by local laboratory												
Pregnancy Test (Urine or Serum β-HCG) [9]	X											
Coagulation Parameters [10, 11]	X											
Hematology and Chemistry [11]	X	X	X	X	X	X	X	X	X	X [12]		
Urinalysis [11]	X					X			X	X [12]		
FT3, FT4 and TSH [11]	X		X		X		X		X	X [12]		
KL-6, β-D glucan [13]												
Laboratory Procedures/Assessments: analysis performed by central laboratory												
Pharmacokinetics [14]	X	X		X				X		X		
Anti-MK-3475 Antibodies [14]	X	X		X				X		X		
Efficacy Measurements												
Tumor Imaging [15]	X				X		X				X	
Digital Photography (if applicable) [16]	X				X		X				X	

1) In general, assessments/procedures are to be performed on Day 1 and prior to the first dose of treatment for each cycle, and the window for each visit is ± 3 days unless otherwise specified. Treatment cycles are 3 weeks (Q3W); however the treatment cycle interval may be increased due to toxicity according to the dose modification guidelines provided in Section 5.2.1.2. If the interval is increased, all procedures except imaging should be performed based on the new dosing schedule.
2) In subjects who discontinue study therapy without documented disease progression, every effort should be made to continue monitoring their disease status by radiologic imagingx every 12 weeks (± 1 week) until (1) the start of new anti-cancer treatment, (2) documented disease progression, (3) death, or (4) the end of the study, whichever occurs first.
3) After the start of new anti-cancer treatment or documented disease progression, the subject should be contacted by telephone every 12 weeks to assess for survival status.
4) Concomitant medications - Enter new medications started during the trial through the Safety Follow-up visit. Record all medications taken for SAE/ECI s as defined in Section 7.2.
5) Record all AEs occurring within 30 days after the last dose of trial treatment. Report all SAEs occurring within 90 days after the last dose of trial treatment or 30 days of the end of treatment if the subject initiates new anticancer therapy, whichever is earlier. Report all ECIs occurring up until 90 days after the last dose of trial treatment or the start of new anti-cancer treatment, whichever comes first. Afterwards, report only SAEs and ECIs that are related to trial treatment. Adverse experiences and laboratory safety measurements will be graded per NCI CTCAE version 4.0. All adverse experiences, whether gradable by CTCAE or not, will also be evaluated for seriousness.
6) Perform physical examinations at predose on the day of the study treatment visit. A full physical examination will be performed at predose of the first dose of trial retreatment and every 3 cycles after Cycle 5.
7) Vital signs to include temperature, pulse, respiratory rate, weight and blood pressure. If a patient's baseline weight does not fluctuate by more than 10%, this weight can be used to calculate dose.
8) ECG should be performed within 30 minutes of the end of infusion after dosing for Cycle 1 and Cycle 8, and 30 day post-discontinuation.
9) For women of reproductive potential, a urine pregnancy test should be performed within 72 hours prior to first dose of trial treatment. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test performed by the local study site laboratory will be required.
10) Coagulation factors (PT/INR and aPTT) should be monitored closely throughout the trial for any subject receiving anticoagulant therapy.
11) Laboratory tests for determining eligibility for Second Course Phase are to be performed locally within 10 days prior to the first dose of trial retreatment. After Cycle 1, lab samples can be collected up to 72 hours prior to the scheduled time point. Following Cycle 6, urinalysis should be performed every 6 cycles and FT3, FT4 and TSH should be performed every 2 cycles. See Section 7.1.3 for details regarding laboratory tests.
12) Unresolved abnormal labs that are drug related AEs should be followed until resolution. Labs do not need to be repeated after the end of treatment if labs are within normal range.
13) KL-6 and β–D glucan will be measured if a subject develops suspected pneumonitis; an additional test may be performed at the descretion of the investigator.
14) A trough (pre-dose) PK sample will be collected at Day 1 of Cycles 1, 2, 4, 8, 9, 13 and 17 (following Cycle 17, every 4 cycles), 30 days after discontinuation of study drug, and 12 weeks and 24 weeks after discontinuation of study drug (or until the subject starts new anti-neoplastic therapy). All trough samples should be drawn within 24 hours before infusion of MK-3475. Anti-MK-3475 antibodies should be drawn with all pre-dose trough PK samples, the 30 day discontinuation draw and 12 weeks and 24 weeks after discontinuation of study drug (or until the subject starts new anti-neoplastic therapy). Procedures for sample collection are described in the Procedures Manual.
15) The Second Course Cycle 1 scan will be performed within 4 weeks prior to restarting with trial treatment in the Second Course Phase after relapse from CR, PR or SD. Imaging should be performed every 6 weeks initially (± 1 week) starting at 12 weeks through 48 weeks, and after 48 weeks, imaging assessments should be performed every 12 weeks (i.e. Cycles 1, 5, 7, 9, 11, 13, 15, 17 and then every 4 cycles [12 weeks]) or more frequently if clinically indicated. Imaging timing should follow calendar days and should not be adjusted for delays in cycle starts or extension of MK-3475 cycle frequencies. The same imaging technique should be used in a subject throughout the trial. Local reading (investigator assessment with site radiology reading) will be used to determine eligibility; Sponsor will collect radiological assessments for retrospective analysis by a central vendor. The processes for image collection and transmission to the central vendor are in the Investigator Imaging Operations Manual (IIOM). After the documentation of progression (if the retreated subject is clinically stable) or response per modified RECIST 1.1 used in this protocol, repeat imaging for confirmation is required. Confirmatory imaging may be performed as early as 4 weeks later; alternately, the scan performed at the next scheduled timepoint may be used as confirmation. CTs should include the chest, abdomen, and pelvis. A chest CT performed for tumor imaging will be used for pulmonary radiographic evaluation.
16) Qualitative digital photography should be performed at baseline and at time of scheduled tumor assessments for cutaneous lesions. Cutaneous lesions are not considered measurable for the purposes of this protocol, but may be considered to be non-target lesions for tumor assessments by investigators. Copies of digital photographs should also be submitted to the central imaging vendor.

7.0 TRIAL PROCEDURES

7.1 Trial Procedures

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

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

7.1.1 Administrative Procedures

7.1.1.1 Informed Consent

The investigator or qualified designee must obtain documented consent from each potential subject or each subject's legally acceptable representative prior to participating in a clinical trial or Future Biomedical Research.

7.1.1.1.1 General Informed Consent

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

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

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

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

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

7.1.1.1.2 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.

7.1.1.2 Inclusion/Exclusion Criteria

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

7.1.1.3 Subject Identification Card

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

7.1.1.4 Medical History

A medical history will be obtained by the investigator. Medical history will include all active conditions, and any condition diagnosed within the prior 10 years that are considered to be clinically significant by the Investigator. Record any prior cancer other than the current cancer evaluated in this study even if diagnosed greater than 10 years prior to the first dose of MK-3475. History of melanoma will be recorded separately and not listed as Medical History.

7.1.1.5 Prior and Concomitant Medications Review

7.1.1.5.1 Prior Medications

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

7.1.1.5.2 Concomitant Medications

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

7.1.1.6 Disease Details and Treatments

7.1.1.6.1 Disease Details

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

7.1.1.6.2 Prior Treatment Details

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

7.1.1.6.3 Subsequent Antineoplastic Therapy Status

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

7.1.1.7 Assignment of Screening Number

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

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

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

7.1.1.8 Assignment of Randomization Number

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

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

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

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

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

7.1.2 Clinical Procedures/Assessments

7.1.2.1 Adverse Event (AE) Monitoring

The investigator will assess each subject to evaluate for potential new or worsening AEs as specified in the Trial Flow Chart and more frequently if clinically indicated. Adverse experiences will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 4.0 (see Appendix 12.5). Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

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

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

7.1.2.2 Physical Exam

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

7.1.2.3 Vital Signs, Height and Weight

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

Patients must be resting in a sitting position for approximately 10 minutes prior to obtaining vital signs. If a patient's baseline weight does not fluctuate by more than 10%, this weight can be used to calculate dose. Height will be measured at screening only.

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

7.1.2.4 12-lead ECG

A standard 12-lead ECG will be performed within 30 minutes of the end of infusion after dosing using local standard procedures as specified in the Trial Flow Chart (Section 6.0) by the investigator. Clinically significant abnormal findings at screening should be recorded as medical history. After the first dose of trial treatment new clinically significant abnormal findings should be recorded as AEs.

7.1.2.5 Eastern Cooperative Oncology Group (ECOG) Performance Scale

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

7.1.3 Laboratory Procedures/Assessments

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

7.1.3.1 Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

Laboratory tests for hematology, chemistry and urinalysis are specified in Table 5.

Table 5 Laboratory Tests

Hematology	**Chemistry**	**Urinalysis**	**Other**
Hematocrit	Albumin	Blood	Serum β-human chorionic gonadotropin (β-hCG)*
Hemoglobin	Alkaline phosphatase	Glucose	PT (INR)
Platelet count	Alanine aminotransferase (ALT)	Protein	aPTT
WBC (total and differential)	Aspartate aminotransferase (AST)	Specific gravity	Free triiodothyronine (FT3)
Red Blood Cell Count	Lactate dehydrogenase (LDH)	Microscopic exam, if abnormal results are noted	Free thyroxine (FT4)
Absolute Neutrophil Count	Creatinine	Urine pregnancy test*	Thyroid stimulating hormone (TSH)
Absolute Lymphocyte Count	Uric Acid		HIV antibody**
	Calcium		HBsAg**
	Chloride		HCV RNA**
	Glucose		KL-6
	Phosphorus		β-D glucan
	Potassium		IgG**
	Sodium		
	Magnesium		
	Total Bilirubin		
	Direct Bilirubin, if total bilirubin is elevated above the upper limit of normal		
	Total protein		
	Blood Urea Nitrogen		

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

Laboratory tests (hematology, serum chemistry, urinalysis, coagulation parameters, thyroid function, KL-6, and β-D glucan) for screening or entry into the Second Course Phase should be performed within 10 days prior to the first dose of treatment. After Cycle 1, pre-dose laboratory procedures can be conducted up to 72 hours prior to dosing. Results must be reviewed by the investigator and found to be acceptable prior to each dose of trial treatment.

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

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

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

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

KL-6 is a lung-specific marker for pneumonitis [19]. β-D glucan is a marker for fungus infectious disease [20], and is used for the differential diagnosis for pneumonitis. KL-6 and β-D glucan will be measured before starting the tratment courses, and thereafter if a subject develops suspected pneumonitis, an additional test will be performed as needed by investigator's judgment.

7.1.3.2 Pharmacokinetic/Pharmacodynamic Evaluations

7.1.3.2.1 Blood Collection for Serum Pharmacokinetics of MK-3475

The timepoints for PK blood sampling are described in Section 6 – Trial Flow Chart. Sample collection, storage and shipment instructions for the samples will be provided in the Procedures Manual.

Every effort should be made to collect blood samples for PK after the discontinuation visit for up to 24 weeks from the last dose of MK-3475 or until start of a new anti-cancer therapy, whichever occurs first.

7.1.3.2.2 Blood Collection for Serum Anti-MK-3475 Antibodies

The timepoints for Anti-MK-3475 Antibodies blood sampling are described in Section 6 – Trial Flow Chart. Sample collection, storage and shipment instructions for the samples will be provided in the Procedures Manual.

Every effort should be made to collect blood samples for anti-MK-3475 antibodies after the discontinuation visit for up to 24 weeks from the last dose of MK-3475 or until start of a new anti-cancer therapy, whichever occurs first.

7.1.3.2.3 Blood Collection for Correlative Studies

Blood for correlative biomarker studies and genetic analysis should be collected as specified in the Trial Flow Chart. Sample collection, storage and shipment instructions for the samples will be provided in the Procedures Manual. The genetic sample should be collected unless there is a documented law or regulation or IRB/IEC ruling prohibiting a required collection for genetic analysis.

7.1.3.3 Future Biomedical Research

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

- Blood for genomics use
- Leftover archival tumor tissue

7.1.3.4 Tumor Imaging and Assessment of Disease

The tumor imaging (CT or MRI) for screening should be performed within 4 weeks prior to the first dose of trial treatment. The site study team must review pre-trial images to confirm the subject has measurable disease per RECIST 1.1. The baseline imaging scan should be submitted to the central imaging vendor for a retrospective analysis of this eligibility criterion. Scans performed as part of routine clinical management are acceptable for use as the screening scan if they are of diagnostic quality and performed within 4 weeks prior to the first dose of trial treatment. The same imaging technique should be used in a subject throughout the study.

Tumor imaging should be performed every 6 calendar weeks (± 1 week) starting at 12 weeks through 48 weeks, and after 48 weeks, imaging assessments should be performed every 12 calendar weeks (± 1 week) (i.e. Screening visit, Cycles 5, 7, 9, 11, 13, 15, 17 and then every 4 cycles [12 weeks]) or more frequently if clinically indicated. Tumor imaging timing should follow calendar days and should not be adjusted for delays in cycle starts or extension of MK-3475 cycle frequencies. Tumor response will be assessed using irRC (See Section 12.6) and the RECIST 1.1 criteria (See Section 12.5) by the central independent radiology review.

After the first documentation of progression per RECIST 1.1, it is at the discretion of the investigator to keep a clinically stable subject on trial treatment or to stop trial treatment until at least 4 weeks later confirms progression or scheduled next confirmatory scan (6 or 12 weeks later from the first documentation of progression). When feasible, subjects should not be discontinued until progression is confirmed per modified RECIST 1.1 criteria, in which a confirmation assessment of disease progression must be obtained at least 4 weeks after the initial disease assessment indicating progressive disease as discussed below in Table 6. Clinically stable is defined by the following criteria:

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

Table 6 Imaging and Treatment after 1st radiologic evidence of PD

	Clinically Stable		Clinically Unstable	
	Imaging	Treatment	Imaging	Treatment
1st radiologic evidence of PD	Repeat imaging at ≥ 4 weeks to confirm PD	May continue study treatment at the Investigator's discretion while awaiting confirmatory scan	Repeat imaging at ≥ 4 weeks to confirm PD if possible	Discontinue treatment
Repeat scan confirms PD	No additional imaging required	Discontinue treatment	No additional imaging required	N/A
Repeat scan shows SD, PR or CR	Continue regularly scheduled imaging assessments every 6 weeks (every 12 weeks after 48 weeks)	Continue study treatment at the Investigator's discretion	Continue regularly scheduled imaging assessments every 6 weeks (every 12 weeks after 48 weeks)	May restart study treatment if condition has improved and/or clinically stable per Investigator's discretion

Subjects that are deemed clinically unstable are not required to have repeat imaging for confirmation. If progression is confirmed, then the subject will be discontinued from trial treatment. If progression is not confirmed, then the subject should resume/continue trial treatment and have their next scan according to the every 6 week schedule (every 12 weeks schedule after 48 weeks).

NOTE: If a subject with confirmed radiographic progression (i.e. 2 scans demonstrating progressive disease) is clinically stable or clinically improved, and there is no further increase in the tumor dimensions at the confirmatory scan, an exception may be considered to continue treatment upon consultation with the Sponsor. Clinically stable subjects should also have at the confirmatory scan no further increase in the target lesions, no unequivocal increase in non-target lesions, and no additional new lesions develop (non-worsening PD) to continue study treatment.

Imaging during the follow-up period is to be repeated every 12 weeks (± 1 week) for subjects who discontinue trial treatment for reasons other than disease progression until the subject experiences confirmed disease progression or starts a new anti-neoplastic therapy.

Local reading (investigator assessment with site radiology reading) based on RECIST 1.1 will be used to determine subject eligibility. The Sponsor will also receive radiologic images for a retrospective analysis of subject eligibility and treatment response to be performed by a central vendor, including RECIST 1.1 and irRC.

7.1.3.5 Photography for Cutaneous Lesions

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

7.1.3.6 Pulmonary Radiographic Evaluation for MK-3475-Induced Pneumonitis

Pulmonary radiographic imaging is used in a diagnosis of MK-3475-induced pneumonitis. A chest CT performed for tumor imaging may be used for pulmonary radiographic evaluation. For a subject with suspected pneumonitis based on respiratory symptoms, other clinical findings or laboratory findings, a chest CT should be performed immediately. If a finding on pneumonitis is observed, the subject should be followed every month with chest imaging to monitor the pneumonitis.

Pulmonary radiographic evaluation will be performed according to the table in Section 6.0. The investigator will judge whether the variation after the study drug administration is an adverse experience or not and record it in the Case Report Form.

Additionally, an independent radiologist will review chest CTs of all subjects for pulmonary radiographic evaluation. For this purpose, the chest CT imaging will be submitted to the SPONSOR.

7.1.3.7 Tumor Tissue Collection

Participation in this trial will require submitting tumor sample for PD-L1 expression evaluation. This specimen will be evaluated at a central laboratory for expression status of PD-L1 by IHC. Tumor tissue for biomarker analysis from an archival tissue sample or newly obtained core or excisional biopsy of a tumor lesion not previously irradiated must be provided at screening. Subjects without archival sample may obtain a new biopsy at the discretion of the investigator. Needle or excisional biopsies, or resected tissue is required. A fine needle aspirate (including EBUS-TBNA), or cytologic specimen will not be acceptable.

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

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

These samples are not required to be obtained within 4 weeks of enrollment. Detailed instructions for tissue collection, processing and shipment are provided in the Procedures Manual. If the subject signs the Future Biomedical Research (FBR) consent, any leftover tissue that would ordinarily be discarded at the end of the study will be retained for FBR.

7.1.4 Other Procedures

7.1.4.1 Withdrawal/Discontinuation

When a subject discontinues/withdraws from participation in the trial, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.2 - Assessing and Recording Adverse Events.

7.1.4.1.1 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 contacting 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 authorities 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.

7.1.4.2 Blinding/Unblinding

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

7.1.4.3 Calibration of Critical Equipment

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

Critical Equipment for this trial includes:

None

7.1.5 Visit Requirements

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

7.1.5.1 Screening

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

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

- Laboratory tests (hematology, serum chemistry, urinalysis, coagulation parameters, thyroid function test, KL-6, and β-D glucan) are to be performed within 10 days prior to the first dose of trial treatment.
- For women of reproductive potential, a urine pregnancy test will be performed within 72 hours prior to the first dose of trial treatment. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required (performed by the local study site laboratory).
- If results of HIV 1/2 antibodies, HBsAg, and HCV RNA (qualitative) test obtained within 3 months before screening are available, they can be used even before consent is obtained.
- Archival tumor biopsy for PD-L1 characterization is not required to be obtained within 4 weeks prior to the first dose of trial treatment.

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

7.1.5.2 Treatment Period

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

7.1.5.2.1 Second Course Phase (Retreatment Period)

Subjects who stop MK-3475 with SD or better may be eligible for up to 1 year of additional MK-3475 therapy if they progress after stopping MK-3745. This retreatment is termed the Second Course Phase of this study and is only available if the study remains open and the subject meets the following conditions:

- Either
    - Stopped initial treatment with MK-3475 after attaining an investigator-determined confirmed CR according to modified RECIST 1.1
        - Was treated for at least 24 weeks with MK-3475 before discontinuing therapy
        - Received at least two treatments with MK-3475 beyond the date when the initial CR was declared

    OR

    - Subject had SD, PR or CR and stopped MK-3475 treatment after 24 months of study therapy for reasons other than disease progression or intolerability

AND

- Experienced an investigator-determined confirmed radiographic disease progression after stopping their initial treatment with MK-3475
- Did not receive any anti-cancer treatment since the last dose of MK-3475
- Have a performance status of 0 or 1 on the ECOG Performance Scale
- Demonstrate adequate organ function as detailed in Section 5.1.2
- Female subject of childbearing potential should have a negative urine or serum pregnancy test within 72 hours prior to receiving retreatment with study medication.

- Female subjects of childbearing potential should be willing to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study medication (Reference Section 5.7.2). Subjects of child bearing potential are those who have not been surgically sterilized or have not been free from menses for > 1 year.
- Male subjects should agree to use an adequate method of contraception starting with the first dose of study therapy through 120 days after the last dose of study therapy.
- Does not have a history or current evidence of any condition, therapy, or laboratory abnormality that might interfere with the subject's participation for the full duration of the trial or is not in the best interest of the subject to participate, in the opinion of the treating investigator.

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

7.1.5.3 Discontinuation

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

7.1.5.4 Post-Treatment Visits

7.1.5.4.1 Safety Follow-Up Visit

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

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

7.1.5.4.2 Follow-up Visits

Subjects who discontinue trial treatment for a reason other than disease progression will move into the Follow-Up Phase and should be assessed every 12 weeks (± 1 week) by radiologic imaging to monitor disease status and collect serum samples for pharmacokinetics and anti-MK-3475 antibodies as specified in the Trial Flow Chart (Section 6.0). Every effort should be made to collect information regarding disease status and serum samples until the start of new anti-neoplastic therapy, disease progression, withdrawal of consent, death, or the end of the study, whichever occurs first. Information regarding post-study anti-neoplastic treatment will be collected if new treatment is initiated.

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

7.1.5.4.3 Survival Follow-up

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

7.2 Assessing and Recording Adverse Events

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

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

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

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

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

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

From the time of treatment allocation/randomization through 30 days following cessation of treatment, all adverse events must be reported by the investigator. Such events will be recorded at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in section 7.2.3.1. The investigator will make every attempt to follow all subjects with non-serious adverse events for outcome.

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

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

For purposes of this trial, an overdose will be defined as any dose exceeding the prescribed dose for MK-3475 by 500% over the prescribed dose (> 10 mg/kg). No specific information is available on the treatment of overdose of MK-3475. In the event of overdose, MK-3475 should be discontinued and the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

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

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

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

7.2.2 Reporting of Pregnancy and Lactation to the Sponsor

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

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

Such events must be reported within 24 hours to the Sponsor either by electronic media or paper. Sponsor Contact information can be found in the Investigator Trial File Binder (or equivalent).

7.2.3 Immediate Reporting of Adverse Events to the Sponsor

7.2.3.1 Serious Adverse Events

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

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

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

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

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

For the time period beginning at treatment allocation/randomization through 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study (reference Section 7.2.3.3 for additional details), whether or not related to the Sponsor's product, must be reported within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

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

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

7.2.3.2 Events of Clinical Interest

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

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

For the time period beginning at treatment allocation/randomization through 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 7.2.1 - Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor, that is not associated with clinical symptoms or abnormal laboratory results.

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

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

3. Additional Adverse Events:

   A separate guidance document has been provided entitled “Event of Clinical Interest Guidance Document” (previously entitled, “Event of Clinical Interest and Immune – Related Adverse Event Guidance Document”). This document can be found in the administrative binder and provides guidance regarding identification, evaluation and management of ECIs and irAEs.

   ECIs (both non-serious and serious adverse events) identified in this guidance document from the date of first dose through 90 days following cessation of treatment, or 30 days after the initiation of a new anticancer therapy, whichever is earlier, need to be reported to the SPONSOR within 24 hours of the event, regardless of attribution to study treatment, consistent with standard SAE reporting guidelines and either by electronic media or paper.Sponsor Contact information can be found in the administrative binder.

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

7.2.3.3 Protocol-Specific Exceptions to Serious Adverse Event Reporting

Efficacy endpoints as outlined in this section will not be reported to the Sponsor as described in Section 7.2.3.- Immediate Reporting of Adverse Events to the Sponsor.

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

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

7.2.4 Evaluating Adverse Events

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

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

Table 7 Evaluating Adverse Events

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

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

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

7.2.5 Sponsor Responsibility for Reporting Adverse Events

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

7.3 TRIAL GOVERNANCE AND OVERSIGHT

7.3.1 Efficacy and Safety Evaluation Committee

The Efficacy and Safety Evaluation Committee (ESEC) will be established for the purpose of evaluating the safety information of this study from the specialist and objective viewpoints to ensure the safety of subjects.

The details of the ESEC are prescribed by separate instructions.

7.3.2 Independent Pulmonary Radiographic Adviser

An independent pulmonary radiographic adviser will review pulmonary radiographic changes and its features using chest CT imaging. The details of the independent pulmonary radiographic adviser are prescribed by separate instructions.

8.0 STATISTICAL ANALYSIS PLAN

8.1 Statistical Analysis Plan Summary

This section contains a brief summary of the statistical analyses for this trial. Full detail is in the Statistical Analysis Plan (SAP) (Section 8.2).

The primary purpose of this study is to investigate the safety, tolerability, and anti-tumor activity of MK-3475 administered intravenously to subjects with advanced melanoma.

8.1.1 Efficacy Analyses

The full analysis set (FAS) population (defined as all subjects with a baseline scan with measurable disease and who either have a post baseline scan or discontinue the trial due to progressive disease or a drug-related AE) will serve as the primary population for the analyses of efficacy data in this trial. Overall response rate based on RECIST 1.1 will be used as the primary endpoint for efficacy assessment. A 95% confidence interval along with a one-sided p-value for testing the null hypothesis (ORR=10%) based on the binomial distribution will be provided for the response rate. The study is considered to have reached the efficacy objective if the corresponding p-value for testing the respective null hypothesis is less than 2.5%. An outline of the efficacy analysis strategy is presented in Table 8 below.

Table 8 Primary Analysis Strategy for Efficacy Endpoints

Endpoint/Variable (Description, Time Point)	Statistical Method	Analysis Population	Missing Data Approach
Primary:			
Overall RECIST 1.1 response rate based on central radiology review	Exact test of binomial parameter	FAS	Subjects with missing data are considered non-responders
Secondary:			
Overall RECIST 1.1 response rate based on site assessment	Exact methods for binomial parameter	FAS	Subjects with missing data are considered non-responders
Progression-free survival (RECIST 1.1)	Summary statistics using Kaplan-Meier method	FAS	Censored at last assessment
Response duration (RECIST 1.1)	Summary statistics using Kaplan-Meier method	All responders	Non-responders are excluded in analysis
Overall survival	Summary statistics using Kaplan-Meier method	FAS	Censored at last assessment
Overall irRC response rate based on central radiology review	Exact methods for binomial parameter	FAS	Subjects with missing data are considered non-responders
Progression-free survival (irRC)	Summary statistics using Kaplan-Meier method	FAS	Censored at last assessment
Response duration (irRC)	Summary statistics using Kaplan-Meier method	All responders	Non-responders are excluded in analysis

8.1.2 Safety Analyses

The All-Patients-as-Treated population will be employed for safety analyses.

8.1.3 Power and Sample Size

In this study, approximately total 35 subjects with advanced melanoma will be enrolled, among them at least 28 from cutaneous melanoma and at most 7 from mucosal melanoma. The at least 28 cutaneous melanoma subjects are the main analysis population. At most 7 subjects with mucosal melanoma are population for exploratory analysis.

With approximately 28 evaluable subjects with advanced cutaneous melanoma, the study has approximately 90% power to detect a 25% difference in ORR under the null hypothesis of ORR=10% with a type I error rate of 2.5% if the true ORR is 35%. Success for this hypothesis requires at least 7/28 responses. The actual number of subjects enrolled may be larger than 28 to ensure that at least 28 subjects are evaluable for main analysis.

8.2 Statistical Analysis Plan

8.2.1 Responsibility for Analyses/In-House Blinding

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

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

The Clinical Biostatistics department will generate the allocation schedule(s) for study treatment assignment.

8.2.2 Hypotheses/Estimation

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

8.2.3 Analysis Endpoints

8.2.3.1 Efficacy/Immunogenicity/Pharmacokinetics Endpoints

Efficacy and safety endpoints that will be evaluated for are listed below, followed by the descriptions of the derivations of selected endpoints.

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

Key secondary efficacy endpoints include:

- Response rate based on site assessments using RECIST 1.1

Other secondary efficacy endpoints include: (1) duration of response, defined as time from first RECIST 1.1 response to disease progression in subjects who achieve a PR or better; (2) progression-free survival (PFS), defined as the time from allocation to the first documented disease progression according to RECIST 1.1 or death due to any cause, whichever occurs first; (3) overall survival (OS) ; (4) Response rate based on irRC ; (5) duration of response based on irRC and (6) progression-free survival (PFS) based on irRC.

Immunogenicity/pharmacokinetics endpoints are exploratory endpoints in this study. Immunogenicity endpoint include anti-MK-3475 antibody and pharmacokinetics endpoints include pharmacokinetic parameters of MK-3475.

8.2.3.2 Safety Endpoints

A description of safety measures is provided in Section 4.2.3.1.

The primary safety endpoints are AEs graded using CTCAE (Version 4.0) criteria. Safety will be assessed by quantifying the toxicities and grades experienced by subjects who have received MK-3475, including serious adverse events (SAEs) and events of clinical interest (ECIs). Immune-related ECIs, as described in Section 7.2.3.2 will be collected. Other safety endpoints include laboratory safety assessments, ECOG performance status, vital signs, 12-lead ECG and physical examinations.

8.2.4 Analysis Populations

8.2.4.1 Efficacy Analysis Populations

The Full Analysis Set (FAS) population will serve as the primary population for the analysis of efficacy data in this study. The FAS population consists of all allocated subjects with subjects excluded for the following reasons:

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

Details on the approach to handling missing data are provided in Section 8.2.5 Statistical Methods.

8.2.4.2 Safety Analysis Populations

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 allocated subjects who received at least one dose of study treatment.

At least one laboratory, 12-lead ECG or vital sign measurement obtained subsequent to at least one dose of study treatment is required for inclusion in the analysis of each specific parameter. To assess change from baseline, a baseline measurement is also required.

Details on the approach to handling missing data for safety analyses are provided in Section 8.2.5 Statistical Methods.

8.2.5 Statistical Methods

Statistical testing and inference for safety analyses are described in 8.2.5.2. Efficacy results that will be considered to be statistically significant after consideration of the strategy for controlling the Type I error are described in Section 8.2.6, Multiplicity. Unless otherwise stated, all statistical tests will be conducted at the α=0.05 (2-sided) level.

8.2.5.1 Statistical Methods for Efficacy Analyses

For the primary efficacy endpoint centrally reviewed RECIST 1.1 response rate, the point estimate, 95% confidence interval, and p-value for testing the RECIST 1.1 response rate is greater than the historical control will be provided using exact binomial distribution. Subjects in the primary analysis population (FAS) without response data will be counted as non-responder.

Secondary efficacy evaluations of RECIST 1.1 response based on investigator assessment will also be conducted using the same methodology as for the primary efficacy analysis.

For PFS endpoint, Kaplan-Meier (KM) curves and median estimates from the KM curves will be provided as appropriate. Subjects without efficacy evaluation data or without survival data will be censored at Day 1. Table 9 summarizes the key efficacy analyses.

Table 9 Analysis Strategy for Key Efficacy Variables

Endpoint/Variable‡ (Description, Time Point)	Primary vs. Supportive Approach†	Statistical Method	Analysis Population	Missing Data Approach
Primary Hypothesis #1				
Overall RECIST 1.1 response by central radiology assessment	P	Exact test of binomial parameter	FAS	Subjects with missing data are considered non-responders
Secondary Hypothesis #1				
Overall RECIST 1.1 response rate based on site assessment	P	Exact methods for binomial parameter	FAS	Subjects with missing data are considered non-responders
Progression-free survival (RECIST 1.1)	P	Summary statistics using Kaplan-Meier method	FAS	Censored at last assessment
Response duration (RECIST 1.1)	P	Summary statistics using Kaplan-Meier method	All responders	Non-responders are excluded in analysis
Overall survival	P	Summary statistics using Kaplan-Meier method	FAS	Censored at last assessment
Overall irRC response rate based on central radiology review	P	Exact methods for binomial parameter	FAS	Subjects with missing data are considered non-responders
Progression-free survival (irRC)	P	Summary statistics using Kaplan-Meier method	FAS	Censored at last assessment
Response duration (irRC)	P	Summary statistics using Kaplan-Meier method	All responders	Non-responders are excluded in analysis

† P=Primary approach; S=Secondary approach.

The strategy to address multiplicity issues with regard to multiple efficacy endpoints is described in Section 8.2.6, Multiplicity and Section 8.2.9, Interim Analyses.

8.2.5.2 Statistical Methods for Safety Analyses

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

Summary statistics (counts, percentage, mean, standard deviation, etc) will be provided for the safety endpoints as appropriate. The 80% confidence interval for the incidence rate of Grade 2 or higher adverse events with an immune etiology and the incidence rate of Grade 4/5 AEs will be provided as appropriate.

8.2.5.3 Summaries of Baseline Characteristics, Demographics, and Other Analyses

Baseline characteristics will be assessed by the use of tables and/or graphs. No statistical hypothesis tests will be performed on these characteristics. The number and percentage of subjects screened, randomized, the primary reasons for screening failure, and the primary reason for discontinuation will be displayed. Demographic variables (e.g., age, gender), baseline characteristics, primary and secondary diagnoses, and prior and concomitant therapies will be summarized either by descriptive statistics or categorical tables.

8.2.5.4 Statistical Methods for Immunogenicity/pharmacokinetics endpoints Analyses

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

Summary statistics will also be provided for anti-MK-3475 antibody.

8.2.6 Multiplicity

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

8.2.7 Sample Size and Power Calculations

In this study, approximately total 35 subjects with advanced melanoma will be enrolled, among them at least 28 from cutaneous melanoma and at most 7 from mucosal melanoma. The 28 cutaneous melanoma subjects are the main analysis population. 7 subjects with mucosal melanoma are population for exploratory analysis.

With approximately 28 evaluable subjects with cutaneous melanoma, the study has approximately 90% power to detect a 25% difference in ORR under the null hypothesis of ORR=10% with a type I error rate of 2.5% if the true ORR is 35%. The null hypothesis rate of 10% is based on the historic response rate in large phase III trials for standard single agent chemotherapy in melanoma [21-30]. Success for this hypothesis requires at least 7/28 responses. The actual number of subjects enrolled may be larger than 28 to ensure that at least 28 subjects are evaluable for primary analysis.

8.2.8 Subgroup Analyses and Effect of Baseline Factors

Same efficacy and safety analysis will be conducted on PD-L1 positive subjects and PD-L1 negative subjects, respectively.

Efficacy and safety analysis will also be conducted on BRAF, NRAS, and c-KIT mutation status.

Although the main target population in this study is subjects with advanced cutaneous melanoma, same efficacy and safety analysis will be conducted on subjects with advanced mucosal melanoma exploratory.

8.2.9 Interim Analyses

No efficacy interim analyses are planned in this trial.

The analysis conducted at the time when all patients are enrolled and have either discontinued or have at least 24 weeks of follow-up since first dose is the main analysis time, if more than 7 /28 responses observed at that time, the trial will declare positive and team will prepare for filing. After the main analysis, the study still follows patients for a longer period of time for duration of response and OS.

8.2.10 Compliance (Medication Adherence)

A day within the study will be considered an On-Therapy day if the subject receives the study medication infusion. The number of Days Should be on Therapy is the total number of days from the first day of study medication to the date of the last dose of study medication. For each subject, percent compliance will then be calculated using the following formula:

$$\text{Percent Compliance} = \frac{\text{Number of Days on Therapy}}{\text{Number of Days Should be on Therapy}} \text{ x } 100.$$

Summary statistics will be provided on percent compliance for the FAS population.

8.2.11 Extent of Exposure

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

9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.1 Investigational Product

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

Clinical Supplies will be provided by the Sponsor as summarized in Table 10.

After the time of the marketing approval of MK-3475, "clinical trial drug" of MK-3475 will be replaced with "post-marketing clinical trial drug". The subjects can receive treatment of MK-3475 as post-marketing clinical trial drug.

Table 10 Product Descriptions

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

9.2 Packaging and Labeling Information

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

Subjects will receive open label vials every 3 weeks (Q3W). Each kit will contain 1 vial.

9.3 Clinical Supplies Disclosure

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

9.4 Storage and Handling Requirements

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

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

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

9.5 Returns and Reconciliation

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

For all trial sites, the local country Sponsor personnel or designee will provide appropriate documentation that must be completed for drug accountability and return.

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

10.1 Confidentiality

10.1.1 Confidentiality of Data

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

10.1.2 Confidentiality of Subject Records

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

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

10.1.3 Confidentiality of Investigator Information

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

1. name, address, telephone number and e-mail address;

2. hospital or clinic address and telephone number;

3. curriculum vitae or other summary of qualifications and credentials; and

4. other professional documentation.

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

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

10.1.4 Confidentiality of IRB/IEC Information

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

10.2 Compliance with Financial Disclosure Requirements

Financial Disclosure requirements are outlined in the US Food and Drug Administration Regulations, Financial Disclosure by Clinical Investigators (21 CFR Part 54). It is the Sponsor's responsibility to determine, based on these regulations, whether a request for Financial Disclosure information is required. It is the investigator's/subinvestigator's responsibility to comply with any such request.

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

10.3 Compliance with Law, Audit and Debarment

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

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

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

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

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

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

The investigator must maintain copies of all documentation and records relating to the conduct of the trial in compliance with all applicable legal and regulatory requirements. This documentation includes, but is not limited to, the protocol, worksheets/case report forms, advertising for subject participation, adverse event reports, subject source data, correspondence with regulatory authorities and IRBs/ERCs, consent forms, investigator's curricula vitae, monitor visit logs, laboratory reference ranges, laboratory certification or quality control procedures and laboratory director curriculum vitae. By signing this protocol, the investigator agrees that documentation shall be retained until at least 2 years after the last approval of a marketing application in an ICH region or until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed

since the formal discontinuation of clinical development of the investigational product. Because the clinical development and marketing application process is variable, it is anticipated that the retention period can be up to 15 years or longer after protocol database lock. The Sponsor will determine the minimum retention period and notify the investigator when documents may be destroyed. The Sponsor will determine the minimum retention period and upon request, will provide guidance to the investigator when documents no longer need to be retained. The sponsor also recognizes that documents may need to be retained for a longer period if required by local regulatory requirements. All trial documents shall be made available if required by relevant regulatory authorities. The investigator must consult with and obtain written approval by the Sponsor prior to destroying trial and/or subject files.

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

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

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

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

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

10.4 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the Sponsor of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to the Clinical Trials Data Bank, http://www.clinicaltrials.gov. Merck, as Sponsor of this trial, will review this protocol and submit the information necessary to fulfill these requirements. Merck entries are not limited to FDAMA/FDAAA mandated trials. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

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

10.5 Quality Management System

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

10.6 Data Management

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

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

10.7 Publications

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

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

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

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

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

11.0 LIST OF REFERENCES

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

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

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

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

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

6. Mu CY, Huang JA, Chen Y, Chen C, Zhang XG. High expression of PD-L1 in lung cancer may contribute to poor prognosis and tumor cells immune escape through suppressing tumor infiltrating dendritic cells maturation. Med Oncol. 2011;28:682-8.

7. Liotta F, Gacci M, Frosali F, uerci V, Vittori G, Lapini A, et al. Frequency of regulatory T cells in peripheral blood and in tumour-infiltrating lymphocytes correlates with poor prognosis in renal cell carcinoma. BJU Intern 2010;107:1500-6.

8. Shoo BA, Kashani-Sabet M. Melanoma arising in African-, Asian-, Latino- and Native-American populations. Semin Cutan Med Surg. 2009;28:96-102.

9. Ferlay J, Shin H-R, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer. 2010;127:2893-917.

10. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin. 2011;61:69-90.

11. Robert C, Thomas L, Bondarenko I, O'Day S, Weber J, Garbe C, et al. Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. N Engl J Med. 2011;364:2517-26.

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

13. Topalian S, Sznol M, McDermott D, Kluger H, Carvajal R, Sharfman W. Safety, Activity, and Immune Correlates of Anti–PD-1 Antibody in Cancer. N Engl J Med. 2012; (366):2443-2454.

14. Omid Hamid. "Preliminary Clinical Efficacy and Safety of MK-3475 (Anti-PD-1 Monoclonal Antibody) in Patients with Advanced Melanoma." Society of Melanoma Research. Los Angeles. 11 November 2012. Conference Presentation.

15. Hamid O, Robert C, Daud A, Hodi FS, Hwu WJ, Kefford R, et al. Safety and Tumor Responses with Lambrolizumab (Anti–PD-1) in Melanoma. New Eng J Med. 2013; 369:134-144.

16. Topalian S, et al. Survival, Durable Tumor Remission, and Long-Term Safety in Patients With Advanced Melanoma Receiving Nivolumab. J Clin Oncol. 2014;32

17. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent R, Ford R, et al. New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228-47.

18. Wolchok JD, Hoos A, O'Day S, Weber JS, Hamid O, Lebbe C, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. Clin Cancer Res 2009; 15: 7412-20.

19. Kohno N, Awaya Y, Oyama T, Yamakido M, Akiyama M, Inoue Y, et al. KL-6, a mucin-like glycoprotein, in bronchoalveolar lavage fluid from patients with interstitial lung disease. Am Rev Respir Dis. 1993; 148:637-42.

20. Obayashi T, Yoshida M, Tamura H, et al. Determination of plasma (1/3)-β-D-glucan: a new diagnostic aid to deep mycosis. J Med Vet Mycol. 1992; 30: 275-80.

21. Flaherty KT, Robert C, Hersey P, Nathan P, Garbe C, Milhem M, et al.Improved survival with MEK inhibition in BRAF-mutated melanoma. N Engl J Med 2012;367:107-14.

22. Hauschild A, Grob JJ, Demidov LV, Jouary T, Gutzmer R, Millward M, et al. Dabrafenib in BRAF-mutated metastatic melanoma: a multicentre, open-label, phase 3 randomised controlled trial. Lancet 2012;380:358-65.

23. Patel PM, Suciu S, Mortier L, Kruit WH, Robert C, Schadendorf D, et al. Extended schedule, escalated dose temozolomide versus dacarbazine in stage IV melanoma: Final results of a randomised phase III study (EORTC 18032). Eur J Cancer. 2011;47:1476-83.

24. Robert C, Thomas L, Bondarenko I, O'Day S, Weber J, Garbe C, et al. Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. N Engl J Med 2011;64:2517-26.

25. Chapman PB, Hauschild A, Robert C, Larkin JMG, Haanen JBAG, Ribas A, et al. Updated overall survival (OS) results for BRIM-3, a phase III randomized, open-label, multicenter trial comparing BRAF inhibitor vemurafenib (vem) with dacarbazine (DTIC) in previously untreated patients with BRAF V600E-mutated melanoma. J Clin Oncol. 30(Suppl 15): (abstract 8502).

26. National Institute for Health and Clinical Excellence. Vemurafenib for treating locally advanced or metastatic BRAF V600 mutation-positive malignant melanoma. 2012.

27. Bedikian AY, Millward M, Pehamberger H, Conry R, Gore M, Trefzer U, et al. Bcl-2 antisense (oblimersen sodium) plus dacarbazine in patients with advanced melanoma: The oblimersen melanoma study group. J Clin Oncol. 2006;24:4738-45.

28. Avril MF, Aamdal S, Grob JJ, Hauschild A, Mohr P, Bonerandi JJ, et al. Fotemustine compared with dacarbazine in patients with disseminated malignant melanoma: A phase III study. J Clin Oncol. 2004;22:1118-25.

29. Middleton MR, Grob JJ, Aaronson N, Fierlbeck G, Tilgen S, Seiter S, et al. Randomized phase III study of temozolomide versus dacarbazine in the treatment of patients with advanced metastatic malignant melanoma. J Clin Oncol. 2000;18:158-66.

30. Chapman PB, Einhorn LH, Meyers ML, saxman S, Destro AN, Panageas KS, et al. Phase III multicenter randomized trial of the dartmouth regimen versus dacarbazine in patients with metastatic melanoma. J Clin Oncol. 1999;17:2745-51.

12.0 APPENDICES

12.1 Merck Code of Conduct for Clinical Trials

Merck*
Code of Conduct for Clinical Trials

I. Introduction

A. Purpose

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

B. Scope

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

II. Scientific Issues

A. Trial Conduct

1. Trial Design

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

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

2. Site Selection

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

3. Site Monitoring/Scientific Integrity

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

B. Publication and Authorship

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

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

III. Subject Protection

A. IRB/ERC review

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

B. Safety

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

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

C. Confidentiality

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

D. Genomic Research

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

IV. Financial Considerations

A. Payments to Investigators

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

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

B. Clinical Research Funding

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

C. Funding for Travel and Other Requests

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

V. Investigator Commitment

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

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

12.2 Collection and Management of Specimens for Future Biomedical Research

1. 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/vaccine response.2

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

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research

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

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/vaccines, 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.

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-trial.

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

A template of each trial 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-trial'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 trial 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.

If specimens are collected for a specific genotype or expression analysis as an objective to the main trial, this analysis is detailed in the main body of this protocol (**Section 8.0 – Statistical Analysis Plan**). These specimens will be processed, analyzed, and the remainder of the specimen will be destroyed. The results of these analyses will be reported along with the other trial results. A separate specimen will be obtained from properly-consented subjects in this protocol for storage in the biorepository for Future Biomedical Research.

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 trial 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 trial 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 trial 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 trial 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 regulatory authorities (e.g., EMEA, FDA), whereby this information would be directly transferred to the regulatory authority.

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-trial. 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. 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 contacting the principal investigator for the main trial. If medical records for the main trial 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 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 authorities 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 can not be processed.

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 authority 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 trial 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.

8. Data Security

Separate databases for specimen information and for results from the Future Biomedical Research sub-trial 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 trial 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-trial will not be used for any other purpose.

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 the trial 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 practice 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 trial 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.

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 trials 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.

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 trial.

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 re-associated 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.

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.

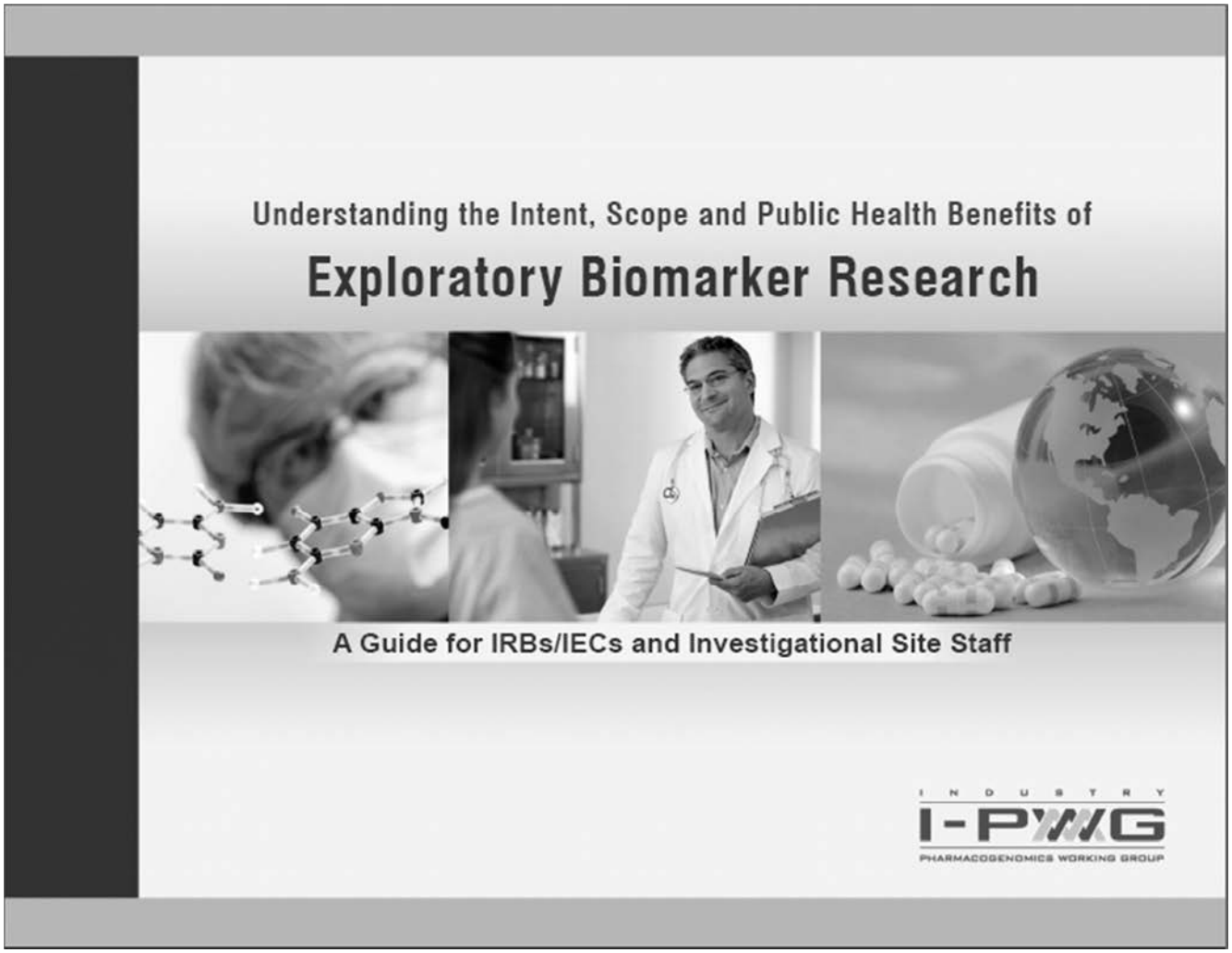
13. Questions

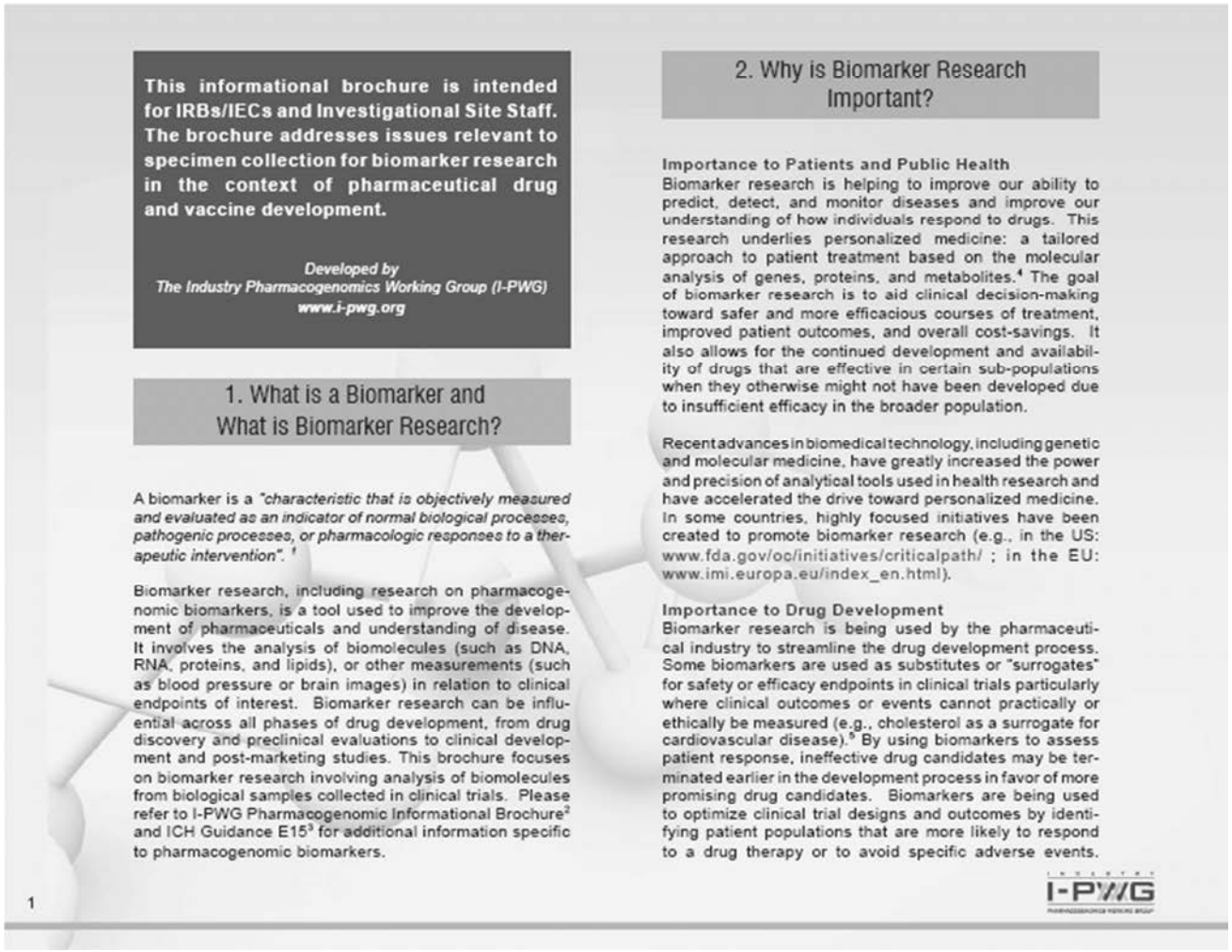
Any questions related to the future biomedical research should be e-mailed directly to clinical.specimen.management@merck.com.

14. References

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

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





This informational brochure is intended for IRBs/IECs and Investigational Site Staff. The brochure addresses issues relevant to specimen collection for biomarker research in the context of pharmaceutical drug and vaccine development.

Developed by
The Industry Pharmacogenomics Working Group (I-PWG)
www.i-pwg.org

1. What is a Biomarker and What is Biomarker Research?

A biomarker is a *"characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention".* [1]

Biomarker research, including research on pharmacogenomic biomarkers, is a tool used to improve the development of pharmaceuticals and understanding of disease. It involves the analysis of biomolecules (such as DNA, RNA, proteins, and lipids), or other measurements (such as blood pressure or brain images) in relation to clinical endpoints of interest. Biomarker research can be influential across all phases of drug development, from drug discovery and preclinical evaluations to clinical development and post-marketing studies. This brochure focuses on biomarker research involving analysis of biomolecules from biological samples collected in clinical trials. Please refer to I-PWG Pharmacogenomic Informational Brochure[2] and ICH Guidance E15[3] for additional information specific to pharmacogenomic biomarkers.

2. Why is Biomarker Research Important?

Importance to Patients and Public Health

Biomarker research is helping to improve our ability to predict, detect, and monitor diseases and improve our understanding of how individuals respond to drugs. This research underlies personalized medicine: a tailored approach to patient treatment based on the molecular analysis of genes, proteins, and metabolites.[4] The goal of biomarker research is to aid clinical decision-making toward safer and more efficacious courses of treatment, improved patient outcomes, and overall cost-savings. It also allows for the continued development and availability of drugs that are effective in certain sub-populations when they otherwise might not have been developed due to insufficient efficacy in the broader population.

Recent advances in biomedical technology, including genetic and molecular medicine, have greatly increased the power and precision of analytical tools used in health research and have accelerated the drive toward personalized medicine. In some countries, highly focused initiatives have been created to promote biomarker research (e.g., in the US: www.fda.gov/oc/initiatives/criticalpath/ ; in the EU: www.imi.europa.eu/index_en.html).

Importance to Drug Development

Biomarker research is being used by the pharmaceutical industry to streamline the drug development process. Some biomarkers are used as substitutes or "surrogates" for safety or efficacy endpoints in clinical trials particularly where clinical outcomes or events cannot practically or ethically be measured (e.g., cholesterol as a surrogate for cardiovascular disease).[5] By using biomarkers to assess patient response, ineffective drug candidates may be terminated earlier in the development process in favor of more promising drug candidates. Biomarkers are being used to optimize clinical trial designs and outcomes by identifying patient populations that are more likely to respond to a drug therapy or to avoid specific adverse events.

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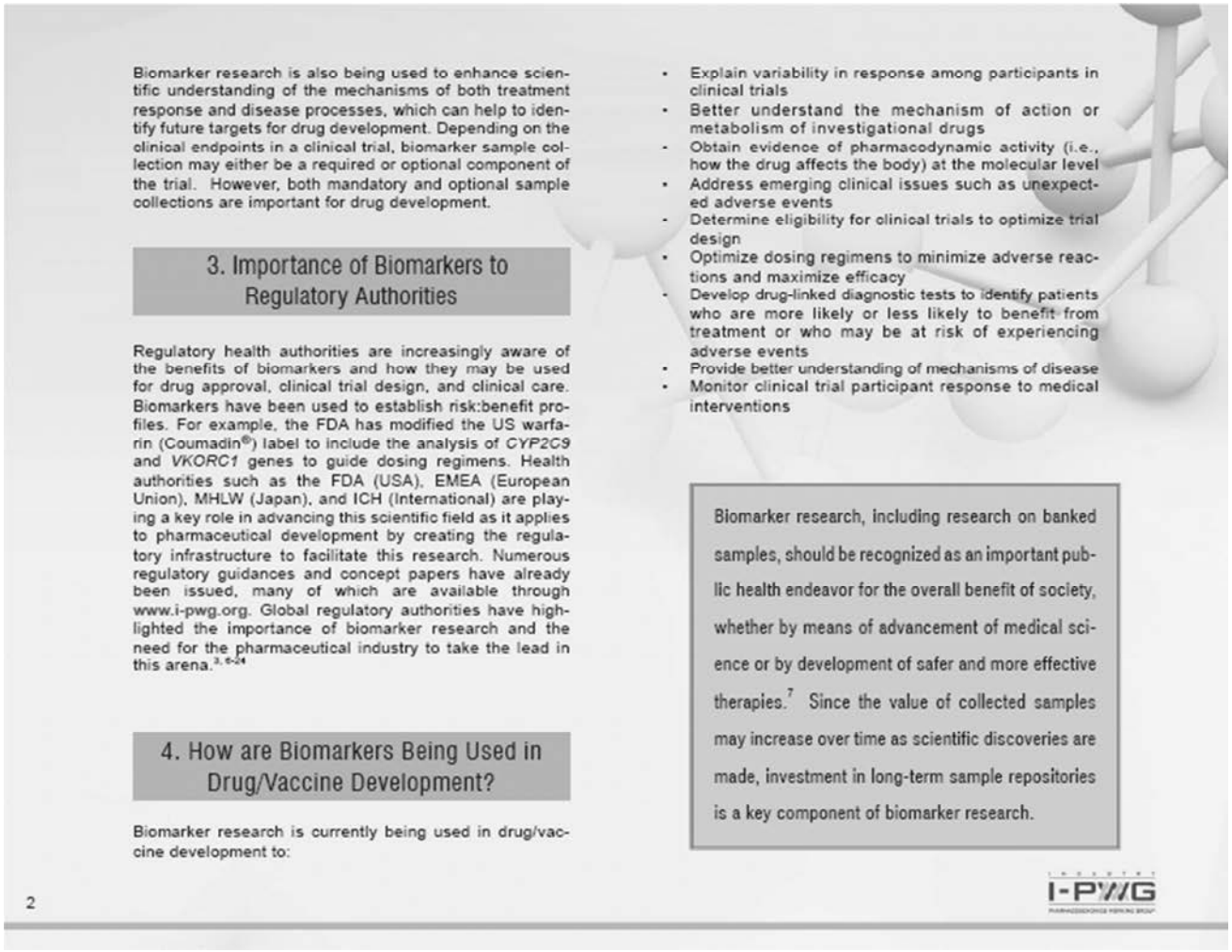

Biomarker research is also being used to enhance scientific understanding of the mechanisms of both treatment response and disease processes, which can help to identify future targets for drug development. Depending on the clinical endpoints in a clinical trial, biomarker sample collection may either be a required or optional component of the trial. However, both mandatory and optional sample collections are important for drug development.

3. Importance of Biomarkers to Regulatory Authorities

Regulatory health authorities are increasingly aware of the benefits of biomarkers and how they may be used for drug approval, clinical trial design, and clinical care. Biomarkers have been used to establish risk:benefit profiles. For example, the FDA has modified the US warfarin (Coumadin®) label to include the analysis of *CYP2C9* and *VKORC1* genes to guide dosing regimens. Health authorities such as the FDA (USA), EMEA (European Union), MHLW (Japan), and ICH (International) are playing a key role in advancing this scientific field as it applies to pharmaceutical development by creating the regulatory infrastructure to facilitate this research. Numerous regulatory guidances and concept papers have already been issued, many of which are available through www.i-pwg.org. Global regulatory authorities have highlighted the importance of biomarker research and the need for the pharmaceutical industry to take the lead in this arena.[3, 6-24]

4. How are Biomarkers Being Used in Drug/Vaccine Development?

Biomarker research is currently being used in drug/vaccine development to:

- Explain variability in response among participants in clinical trials
- Better understand the mechanism of action or metabolism of investigational drugs
- Obtain evidence of pharmacodynamic activity (i.e., how the drug affects the body) at the molecular level
- Address emerging clinical issues such as unexpected adverse events
- Determine eligibility for clinical trials to optimize trial design
- Optimize dosing regimens to minimize adverse reactions and maximize efficacy
- Develop drug-linked diagnostic tests to identify patients who are more likely or less likely to benefit from treatment or who may be at risk of experiencing adverse events
- Provide better understanding of mechanisms of disease
- Monitor clinical trial participant response to medical interventions

Biomarker research, including research on banked samples, should be recognized as an important public health endeavor for the overall benefit of society, whether by means of advancement of medical science or by development of safer and more effective therapies.[7] Since the value of collected samples may increase over time as scientific discoveries are made, investment in long-term sample repositories is a key component of biomarker research.

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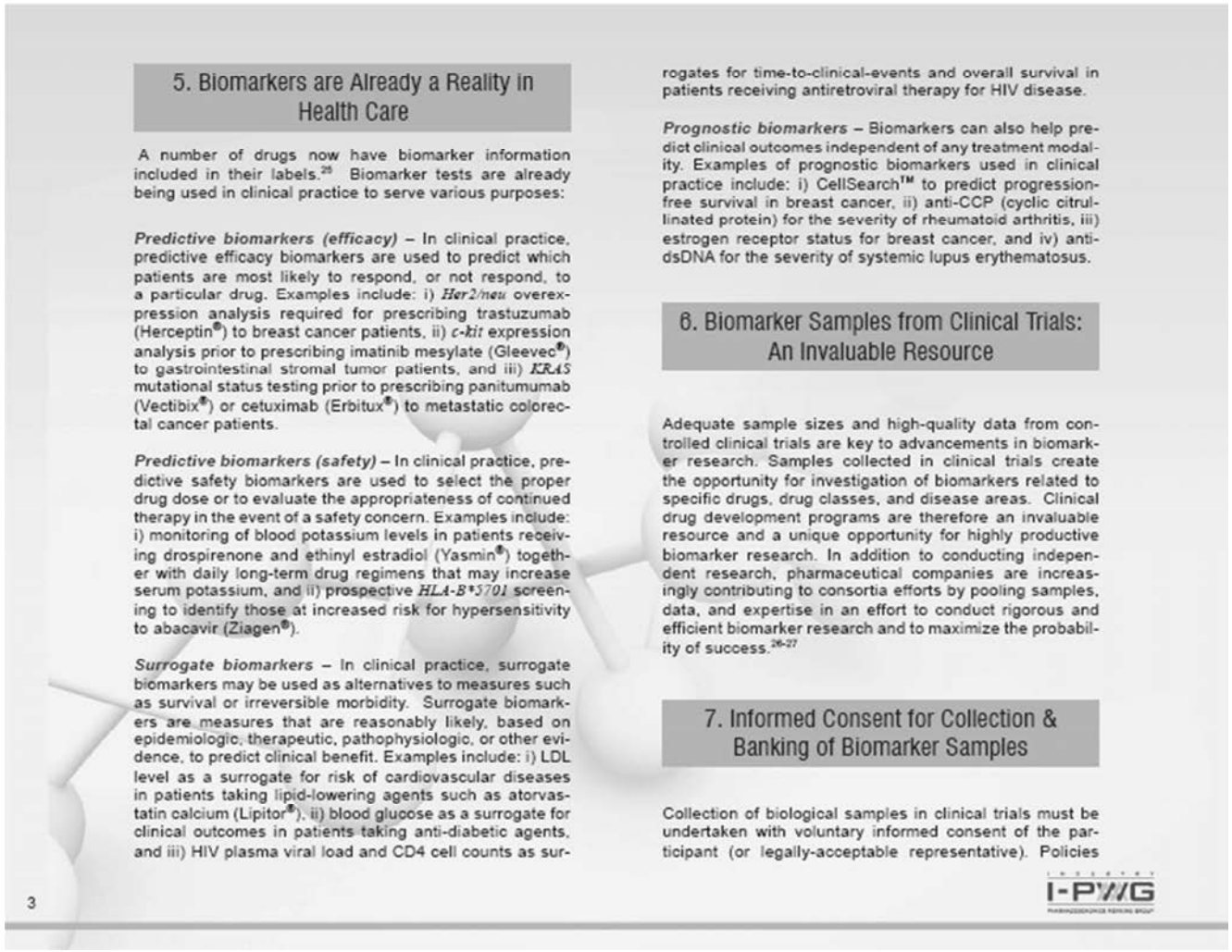

5. Biomarkers are Already a Reality in Health Care

A number of drugs now have biomarker information included in their labels.[25] Biomarker tests are already being used in clinical practice to serve various purposes:

Predictive biomarkers (efficacy) – In clinical practice, predictive efficacy biomarkers are used to predict which patients are most likely to respond, or not respond, to a particular drug. Examples include: i) *Her2/neu* overexpression analysis required for prescribing trastuzumab (Herceptin®) to breast cancer patients, ii) *c-kit* expression analysis prior to prescribing imatinib mesylate (Gleevec®) to gastrointestinal stromal tumor patients, and iii) *KRAS* mutational status testing prior to prescribing panitumumab (Vectibix®) or cetuximab (Erbitux®) to metastatic colorectal cancer patients.

Predictive biomarkers (safety) – In clinical practice, predictive safety biomarkers are used to select the proper drug dose or to evaluate the appropriateness of continued therapy in the event of a safety concern. Examples include: i) monitoring of blood potassium levels in patients receiving drospirenone and ethinyl estradiol (Yasmin®) together with daily long-term drug regimens that may increase serum potassium, and ii) prospective *HLA-B*5701* screening to identify those at increased risk for hypersensitivity to abacavir (Ziagen®).

Surrogate biomarkers – In clinical practice, surrogate biomarkers may be used as alternatives to measures such as survival or irreversible morbidity. Surrogate biomarkers are measures that are reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit. Examples include: i) LDL level as a surrogate for risk of cardiovascular diseases in patients taking lipid-lowering agents such as atorvastatin calcium (Lipitor®), ii) blood glucose as a surrogate for clinical outcomes in patients taking anti-diabetic agents, and iii) HIV plasma viral load and CD4 cell counts as surrogates for time-to-clinical-events and overall survival in patients receiving antiretroviral therapy for HIV disease.

Prognostic biomarkers – Biomarkers can also help predict clinical outcomes independent of any treatment modality. Examples of prognostic biomarkers used in clinical practice include: i) CellSearch™ to predict progression-free survival in breast cancer, ii) anti-CCP (cyclic citrullinated protein) for the severity of rheumatoid arthritis, iii) estrogen receptor status for breast cancer, and iv) anti-dsDNA for the severity of systemic lupus erythematosus.

6. Biomarker Samples from Clinical Trials: An Invaluable Resource

Adequate sample sizes and high-quality data from controlled clinical trials are key to advancements in biomarker research. Samples collected in clinical trials create the opportunity for investigation of biomarkers related to specific drugs, drug classes, and disease areas. Clinical drug development programs are therefore an invaluable resource and a unique opportunity for highly productive biomarker research. In addition to conducting independent research, pharmaceutical companies are increasingly contributing to consortia efforts by pooling samples, data, and expertise in an effort to conduct rigorous and efficient biomarker research and to maximize the probability of success.[26-27]

7. Informed Consent for Collection & Banking of Biomarker Samples

Collection of biological samples in clinical trials must be undertaken with voluntary informed consent of the participant (or legally-acceptable representative). Policies

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and regulations for legally-appropriate informed consent vary on national, state, and local levels, but are generally based on internationally recognized pillars of ethical conduct for research on human subjects.[26-31]

Optional vs. Required Subject Participation

Depending on the relevance of biomarker research to a clinical development program at the time of protocol development, the biomarker research may be a core required component of a trial (e.g., key to elucidating the drug mechanism of action or confirming that the drug is interacting with the target) or may be optional (e.g., to gain valuable knowledge that enhances the understanding of diseases and drugs). Informed consent for the collection of biomarker samples may be presented either in the main clinical informed consent form or as a separate informed consent form, with approaches varying somewhat across pharmaceutical companies. The relevance of biomarker research to a clinical development program may change over time as the science evolves. The samples may therefore increase in value after a protocol is developed.

Consent for Future Research Use

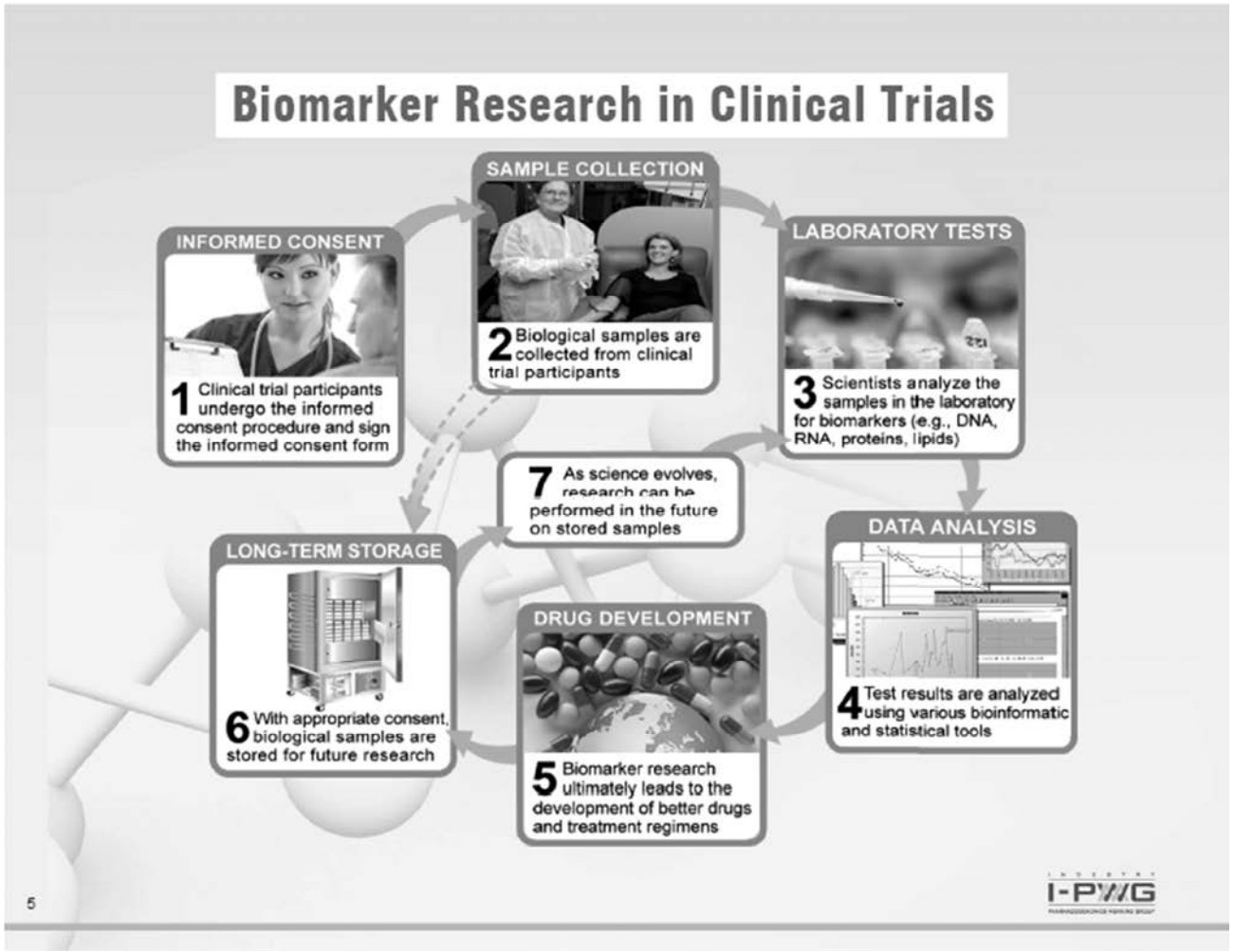
While it can be a challenge to specify the details of the research that will be conducted in the future, the I-PWG holds the view that future use of samples collected for exploratory biomarker research in clinical trials should be permissible when i) the research is scientifically sound, ii) participants are informed of the scope of the intended future research, even if this is broadly defined (see potential uses in Section 4 above), iii) autonomy is respected by providing the option to consent separately to future use of samples or by providing the option to terminate further use of samples upon request (consent withdrawal / sample destruction), and iv) industry standards for confidentiality protection per Good Clinical Practice guidelines are met.[3, 31] Importantly, any research using banked samples should be consistent with the original informed consent, except where otherwise permitted by local law or regulation.

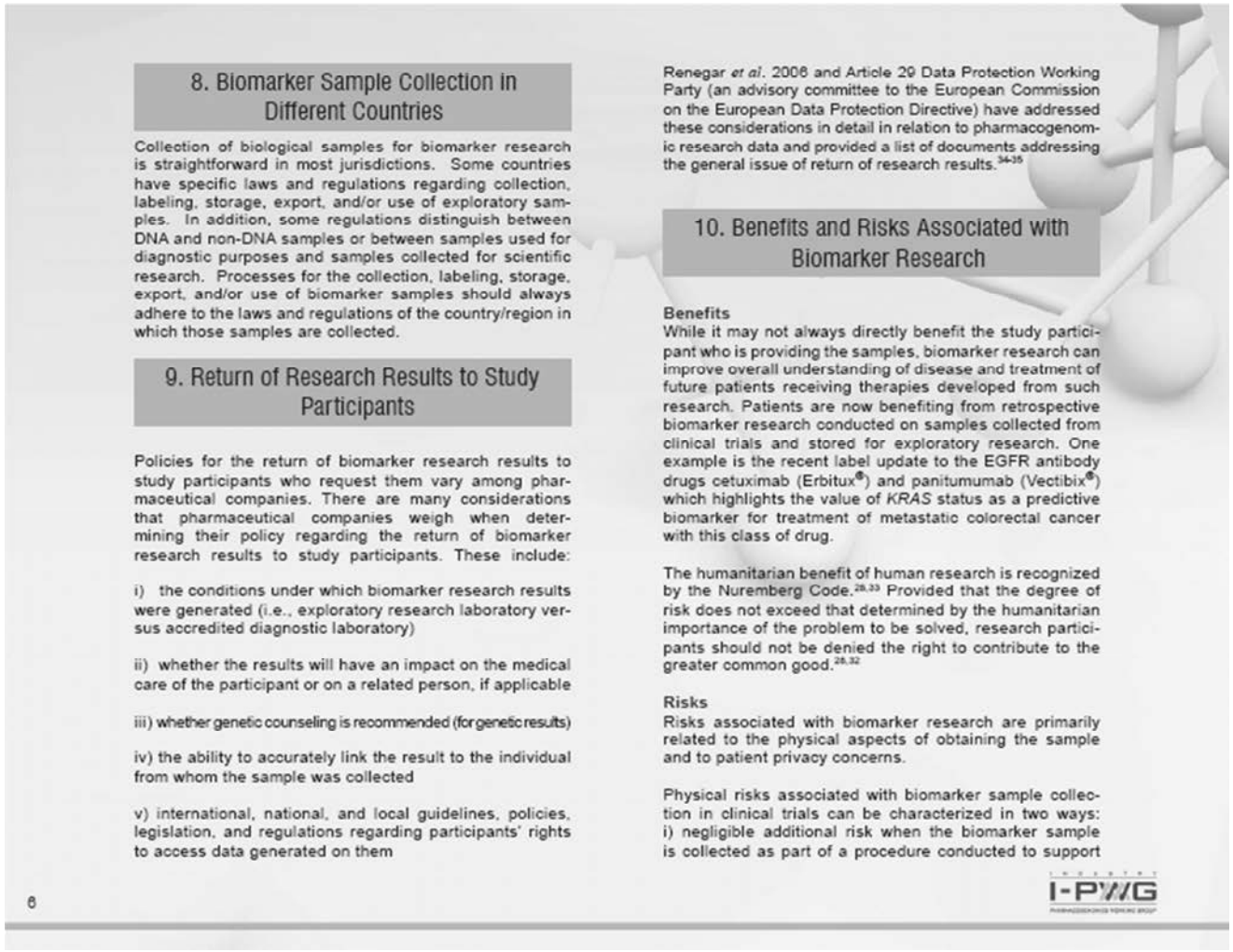
Important elements of informed consent for **future use** of samples include, but are not limited to:[39]

The scope of research – Where the scope of the potential future research is broad, participants should be informed of the boundaries of the research. While it may not be possible to describe the exact analytical techniques that will be used, or specific molecules that will be analyzed, it is possible to clearly articulate in reasonable detail the type of research to be conducted and its purpose. Information regarding whether stored samples may be shared with other parties or utilized for commercialization purposes should also be addressed.

Withdrawal of consent / sample destruction – The informed consent form should inform participants of their right to withdraw their consent / request destruction of their samples. This should include the mechanisms for exercising that right and any limitations to exercising that right. For example, participants should be informed that it is not possible to destroy samples that have been anonymized.[3] In addition, according to industry standards and regulatory guidance, participants should be informed that data already generated prior to a consent withdrawal request are to be maintained as part of the study data.[38]

The duration of storage – The permissible duration of storage may vary according to the nature and uses of the samples and may also vary on national, state, and local levels. The intended duration of storage, including indefinite storage, should be specified.


Biomarker Research in Clinical Trials
SAMPLE COLLECTION
2 Biological samples are collected from clinical trial participants
LABORATORY TESTS
3 Scientists analyze the samples in the laboratory for biomarkers (e.g., DNA, RNA, proteins, lipids)
INFORMED CONSENT
1 Clinical trial participants undergo the informed consent procedure and sign the informed consent form
7 As science evolves, research can be performed in the future on stored samples
DATA ANALYSIS
4 Test results are analyzed using various bioinformatic and statistical tools
LONG-TERM STORAGE
6 With appropriate consent, biological samples are stored for future research
DRUG DEVELOPMENT
5 Biomarker research ultimately leads to the development of better drugs and treatment regimens
5
I-PWG



8. Biomarker Sample Collection in Different Countries

Collection of biological samples for biomarker research is straightforward in most jurisdictions. Some countries have specific laws and regulations regarding collection, labeling, storage, export, and/or use of exploratory samples. In addition, some regulations distinguish between DNA and non-DNA samples or between samples used for diagnostic purposes and samples collected for scientific research. Processes for the collection, labeling, storage, export, and/or use of biomarker samples should always adhere to the laws and regulations of the country/region in which those samples are collected.

9. Return of Research Results to Study Participants

Policies for the return of biomarker research results to study participants who request them vary among pharmaceutical companies. There are many considerations that pharmaceutical companies weigh when determining their policy regarding the return of biomarker research results to study participants. These include:

i) the conditions under which biomarker research results were generated (i.e., exploratory research laboratory versus accredited diagnostic laboratory)

ii) whether the results will have an impact on the medical care of the participant or on a related person, if applicable

iii) whether genetic counseling is recommended (for genetic results)

iv) the ability to accurately link the result to the individual from whom the sample was collected

v) international, national, and local guidelines, policies, legislation, and regulations regarding participants' rights to access data generated on them

Renegar *et al*. 2008 and Article 29 Data Protection Working Party (an advisory committee to the European Commission on the European Data Protection Directive) have addressed these considerations in detail in relation to pharmacogenomic research data and provided a list of documents addressing the general issue of return of research results.[34-35]

10. Benefits and Risks Associated with Biomarker Research

Benefits

While it may not always directly benefit the study participant who is providing the samples, biomarker research can improve overall understanding of disease and treatment of future patients receiving therapies developed from such research. Patients are now benefiting from retrospective biomarker research conducted on samples collected from clinical trials and stored for exploratory research. One example is the recent label update to the EGFR antibody drugs cetuximab (Erbitux®) and panitumumab (Vectibix®) which highlights the value of *KRAS* status as a predictive biomarker for treatment of metastatic colorectal cancer with this class of drug.

The humanitarian benefit of human research is recognized by the Nuremberg Code.[28,33] Provided that the degree of risk does not exceed that determined by the humanitarian importance of the problem to be solved, research participants should not be denied the right to contribute to the greater common good.[28,32]

Risks

Risks associated with biomarker research are primarily related to the physical aspects of obtaining the sample and to patient privacy concerns.

Physical risks associated with biomarker sample collection in clinical trials can be characterized in two ways: i) negligible additional risk when the biomarker sample is collected as part of a procedure conducted to support

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other core trial objectives, and ii) some added risk where the sampling procedure would otherwise have not been performed as a core component of a trial. Risks are also determined by the invasiveness of the sample collection procedure.

Privacy risks are generally those associated with the inappropriate disclosure and misuse of data. Pharmaceutical companies have policies and procedures for confidentiality protection to minimize this risk for all data collected and generated in clinical trials. These may vary across companies, but are based on industry standards of confidentiality and privacy protection highlighted in the following section. Importantly, privacy risks inherent to biomarker data are no greater than other data collected in a clinical trial.

11. Privacy, Confidentiality, and Patient Rights

Maintaining the privacy of study participants and the confidentiality of information relating to them is of paramount concern to industry researchers, regulators, and patients. Good Clinical Practice (GCP), the standard adhered to in pharmaceutical clinical research, is a standard that

"...provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected",

where confidentiality is defined as, *"The prevention of disclosure, to other than authorized individuals, of a sponsor's proprietary information or of a subject's identity."*

This standard dictates that *"the confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with applicable regulatory requirements."* [31]

Exploratory biomarker research in pharmaceutical development is commonly conducted in research laboratories that are not accredited to perform diagnostic tests used for healthcare decision-making. Therefore, results from exploratory biomarker research usually are not appropriate for use in making decisions about a trial participant's health. In addition, exploratory research data should not be included as part of a participant's medical record accessible for use by insurance companies. Legislation and policies to protect individuals against discrimination based on genetic information continually evolve based on social, ethical, and legal considerations. Examples of such legislation include the Human Tissue Act 2004 (UK) and the Genetic Information Nondiscrimination Act (GINA) 2008 (USA).[36-37]

12.Where to Get More Information?

Educational resources related to biomarker and pharmacogenomic research that caters to health care professionals, IRBs/IECs, scientists, and patients are continually being created and are publicly available. Links to many of these resources are available through the I-PWG website: www.i-pwg.org.

13. What is I-PWG?

The Industry Pharmacogenomics Working Group (I-PWG) (formerly the Pharmacogenetics Working Group) is a voluntary association of pharmaceutical companies engaged in pharmacogenomic research. The Group's activities focus on non-competitive educational, informational, ethical, legal, and regulatory topics. The Group provides information and expert opinions on these topics and sponsors educational/informational programs to promote better understanding of pharmacogenomic and other biomarker research for key stakeholders. The I-PWG interacts with regulatory author-

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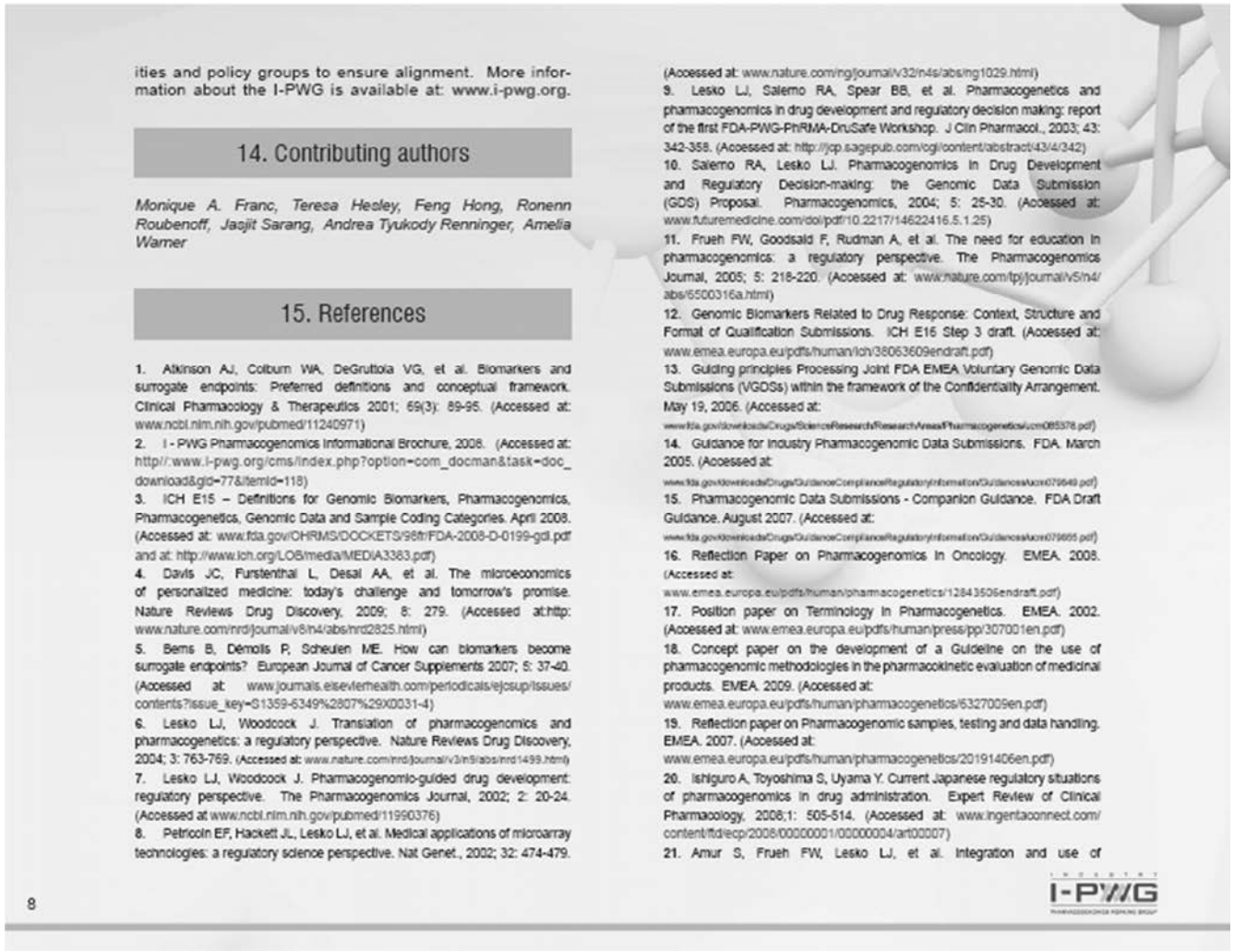

ities and policy groups to ensure alignment. More information about the I-PWG is available at: www.i-pwg.org.

14. Contributing authors

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15. References

1. Atkinson AJ, Colburn WA, DeGruttola VG, et al. Biomarkers and surrogate endpoints: Preferred definitions and conceptual framework. Clinical Pharmacology & Therapeutics 2001; 69(3): 89-95. (Accessed at: www.ncbi.nlm.nih.gov/pubmed/11240971)
2. I - PWG Pharmacogenomics Informational Brochure, 2008. (Accessed at: http//:www.i-pwg.org/cms/index.php?option=com_docman&task=doc_download&gid=77&Itemid=118)
3. ICH E15 – Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories. April 2008. (Accessed at: www.fda.gov/OHRMS/DOCKETS/98fr/FDA-2008-D-0199-gdl.pdf and at: http://www.ich.org/LOB/media/MEDIA3383.pdf)
4. Davis JC, Furstenthal L, Desai AA, et al. The microeconomics of personalized medicine: today's challenge and tomorrow's promise. Nature Reviews Drug Discovery, 2009; 8: 279. (Accessed at:http: www.nature.com/nrd/journal/v8/n4/abs/nrd2825.html)
5. Bems B, Demolis P, Scheulen ME. How can biomarkers become surrogate endpoints? European Journal of Cancer Supplements 2007; 5: 37-40. (Accessed at: www.journals.elsevierhealth.com/periodicals/ejcsup/issues/contents?issue_key=S1359-6349%2807%29X0031-4)
6. Lesko LJ, Woodcock J. Translation of pharmacogenomics and pharmacogenetics: a regulatory perspective. Nature Reviews Drug Discovery, 2004; 3: 763-769. (Accessed at: www.nature.com/nrd/journal/v3/n9/abs/nrd1499.html)
7. Lesko LJ, Woodcock J. Pharmacogenomic-guided drug development: regulatory perspective. The Pharmacogenomics Journal, 2002; 2: 20-24. (Accessed at:www.ncbi.nlm.nih.gov/pubmed/11990376)
8. Petricoin EF, Hackett JL, Lesko LJ, et al. Medical applications of microarray technologies: a regulatory science perspective. Nat Genet., 2002; 32: 474-479. (Accessed at: www.nature.com/ng/journal/v32/n4s/abs/ng1029.html)
9. Lesko LJ, Salerno RA, Spear BB, et al. Pharmacogenetics and pharmacogenomics in drug development and regulatory decision making: report of the first FDA-PWG-PhRMA-DruSafe Workshop. J Clin Pharmacol., 2003; 43: 342-358. (Accessed at: http://jcp.sagepub.com/cgi/content/abstract/43/4/342)
10. Salerno RA, Lesko LJ. Pharmacogenomics in Drug Development and Regulatory Decision-making: the Genomic Data Submission (GDS) Proposal. Pharmacogenomics, 2004; 5: 25-30. (Accessed at: www.futuremedicine.com/doi/pdf/10.2217/14622416.5.1.25)
11. Frueh FW, Goodsaid F, Rudman A, et al. The need for education in pharmacogenomics: a regulatory perspective. The Pharmacogenomics Journal, 2005; 5: 218-220. (Accessed at: www.nature.com/tpj/journal/v5/n4/abs/6500316a.html)
12. Genomic Biomarkers Related to Drug Response: Context, Structure and Format of Qualification Submissions. ICH E16 Step 3 draft. (Accessed at: www.emea.europa.eu/pdfs/human/ich/38063609endraft.pdf)
13. Guiding principles Processing Joint FDA EMEA Voluntary Genomic Data Submissions (VGDSs) within the framework of the Confidentiality Arrangement. May 19, 2006. (Accessed at: www.fda.gov/downloads/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm085378.pdf)
14. Guidance for Industry Pharmacogenomic Data Submissions. FDA. March 2005. (Accessed at: www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079849.pdf)
15. Pharmacogenomic Data Submissions - Companion Guidance. FDA Draft Guidance. August 2007. (Accessed at: www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079905.pdf)
16. Reflection Paper on Pharmacogenomics in Oncology. EMEA. 2008. (Accessed at: www.emea.europa.eu/pdfs/human/pharmacogenetics/12843506endraft.pdf)
17. Position paper on Terminology in Pharmacogenetics. EMEA. 2002. (Accessed at: www.emea.europa.eu/pdfs/human/press/pp/307001en.pdf)
18. Concept paper on the development of a Guideline on the use of pharmacogenomic methodologies in the pharmacokinetic evaluation of medicinal products. EMEA. 2009. (Accessed at: www.emea.europa.eu/pdfs/human/pharmacogenetics/6327009en.pdf)
19. Reflection paper on Pharmacogenomic samples, testing and data handling. EMEA. 2007. (Accessed at: www.emea.europa.eu/pdfs/human/pharmacogenetics/20191406en.pdf)
20. Ishiguro A, Toyoshima S, Uyama Y. Current Japanese regulatory situations of pharmacogenomics in drug administration. Expert Review of Clinical Pharmacology, 2008;1: 505-514. (Accessed at: www.ingentaconnect.com/content/ftd/ecp/2008/00000001/00000004/art00007)
21. Amur S, Frueh FW, Lesko LJ, et al. Integration and use of

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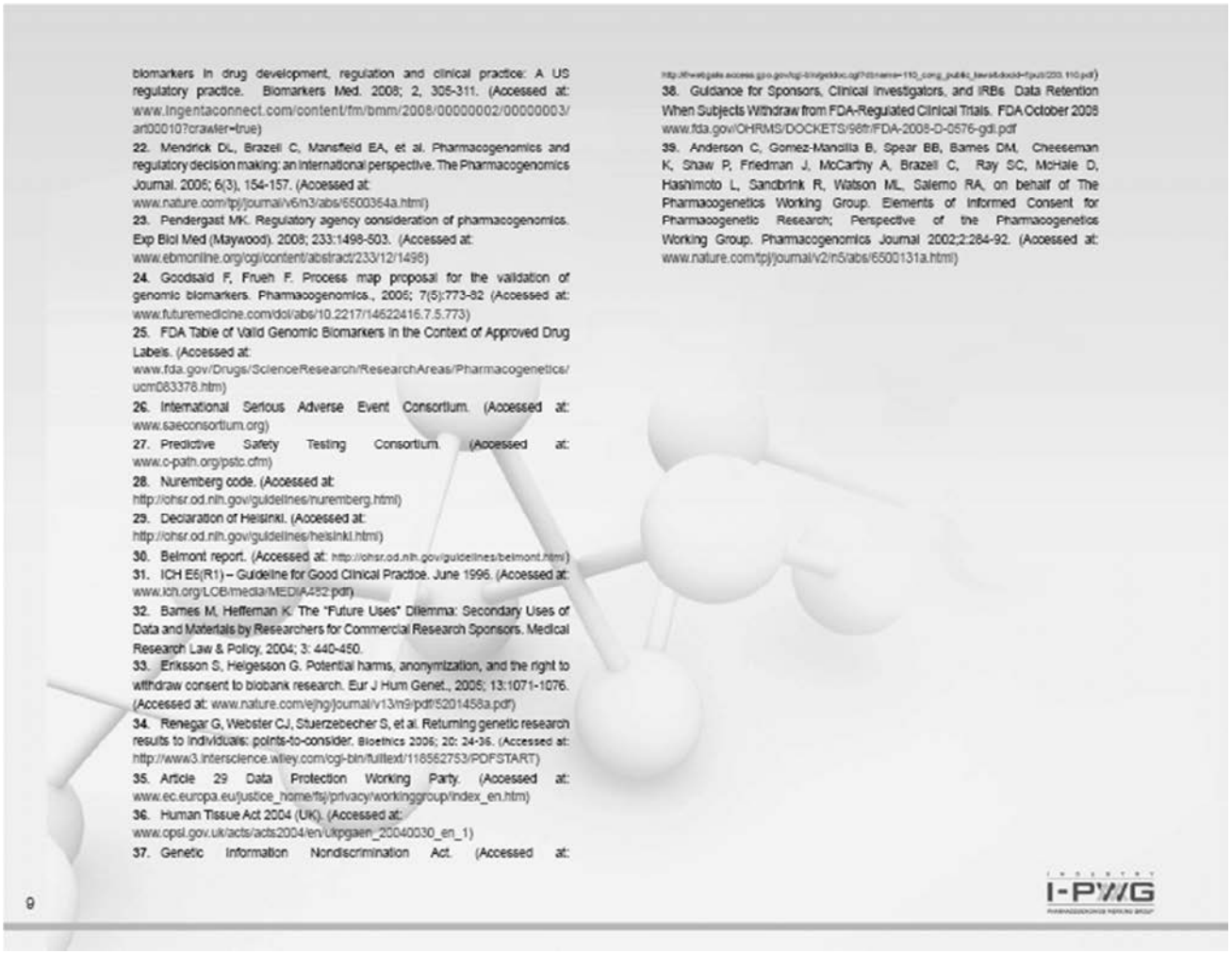

biomarkers in drug development, regulation and clinical practice: A US regulatory practice. Biomarkers Med. 2008; 2, 305-311. (Accessed at: www.ingentaconnect.com/content/fm/bmm/2008/00000002/00000003/art00010?crawler=true)
22. Mendrick DL, Brazell C, Mansfield EA, et al. Pharmacogenomics and regulatory decision making: an international perspective. The Pharmacogenomics Journal. 2006; 6(3), 154-157. (Accessed at: www.nature.com/tpj/journal/v6/n3/abs/6500364a.html)
23. Pendergast MK. Regulatory agency consideration of pharmacogenomics. Exp Biol Med (Maywood). 2008; 233:1498-503. (Accessed at: www.ebmonline.org/cgi/content/abstract/233/12/1498)
24. Goodsaid F, Frueh F. Process map proposal for the validation of genomic biomarkers. Pharmacogenomics., 2006; 7(5):773-82 (Accessed at: www.futuremedicine.com/doi/abs/10.2217/14622416.7.5.773)
25. FDA Table of Valid Genomic Biomarkers in the Context of Approved Drug Labels. (Accessed at: www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm)
26. International Serious Adverse Event Consortium. (Accessed at: www.saeconsortium.org)
27. Predictive Safety Testing Consortium. (Accessed at: www.c-path.org/pstc.cfm)
28. Nuremberg code. (Accessed at: http://ohsr.od.nih.gov/guidelines/nuremberg.html)
29. Declaration of Helsinki. (Accessed at: http://ohsr.od.nih.gov/guidelines/helsinki.html)
30. Belmont report. (Accessed at: http://ohsr.od.nih.gov/guidelines/belmont.html)
31. ICH E6(R1) – Guideline for Good Clinical Practice. June 1996. (Accessed at: www.ich.org/LOB/media/MEDIA482.pdf)
32. Barnes M, Heffernan K. The "Future Uses" Dilemma: Secondary Uses of Data and Materials by Researchers for Commercial Research Sponsors. Medical Research Law & Policy, 2004; 3: 440-450.
33. Eriksson S, Helgesson G. Potential harms, anonymization, and the right to withdraw consent to biobank research. Eur J Hum Genet., 2006; 13:1071-1076. (Accessed at: www.nature.com/ejhg/journal/v13/n9/pdf/5201458a.pdf)
34. Renegar G, Webster CJ, Stuerzebecher S, et al. Returning genetic research results to individuals: points-to-consider. Bioethics 2006; 20: 24-36. (Accessed at: http://www3.interscience.wiley.com/cgi-bin/fulltext/118562753/PDFSTART)
35. Article 29 Data Protection Working Party. (Accessed at: www.ec.europa.eu/justice_home/fsj/privacy/workinggroup/index_en.htm)
36. Human Tissue Act 2004 (UK). (Accessed at: www.opsi.gov.uk/acts/acts2004/en/ukpgaen_20040030_en_1)
37. Genetic Information Nondiscrimination Act. (Accessed at: http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=110_cong_public_laws&docid=f:pu1233.110.pdf)
38. Guidance for Sponsors, Clinical Investigators, and IRBs Data Retention When Subjects Withdraw from FDA-Regulated Clinical Trials. FDA October 2008 www.fda.gov/OHRMS/DOCKETS/98fr/FDA-2008-D-0576-gdl.pdf
39. Anderson C, Gomez-Mancilla B, Spear BB, Barnes DM, Cheeseman K, Shaw P, Friedman J, McCarthy A, Brazell C, Ray SC, McHale D, Hashimoto L, Sandbrink R, Watson ML, Salerno RA, on behalf of The Pharmacogenetics Working Group. Elements of Informed Consent for Pharmacogenetic Research; Perspective of the Pharmacogenetics Working Group. Pharmacogenomics Journal 2002;2:284-92. (Accessed at: www.nature.com/tpj/journal/v2/n5/abs/6500131a.html)


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12.4 ECOG Performance Status

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

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

12.5 Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 Criteria For Evaluating Response in Solid Tumors

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

*REFERENCE:

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

12.6 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, whichever is greater. 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 or 2 times the axial slice thickness. 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 or two times the axial slice thickness.
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 (≥ 5 X 5 mm; up to 5 new lesions per organ: 5 new cutaneous lesions and 10 visceral 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).

*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. Clin Cancer Res. 2009;15:7412-20.

12.7 Clinical Study Conduct System

Clinical study conduct system in Japan is provided in Attachment by Japanese language.

13.0 SIGNATURES

13.1 Sponsor's Representative

TYPED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	

13.2 Investigator

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

TYPED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	