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One Merck Drive
P.O. Box 100
Whitehouse Station, NJ 08889-0100, U.S.A.

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TITLE:

A Multinational, Multicenter, Phase III, Randomized Open-label Trial of Pembrolizumab versus Docetaxel in Previously Treated Subjects with Non-Small Cell Lung Cancer

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DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Amendment 05	14-JUL-2021	To add standard extension study language, update contraception language, and updated the dose modification table.
Amendment 04	1-OCT-2018	Amendment
Amendment 03	19-DEC-2017	Amendment
Amendment 02	15-MAR-2017	Amendment
Amendment 01	30-AUG-2016	Amendment
Original Protocol	15-APR-2016	Original Protocol

SUMMARY OF CHANGES

PRIMARY REASON(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
1.0	Trial Summary/Duration of Participation	Added: Once the subject has achieved the study objective or the study has ended, the subject is discontinued from the study and may be enrolled in an extension study to continue protocol defined assessments and treatment.	To include the extension study.
2.2	Trial Diagram	Added: Study Completion and Pembrolizumab Extension Study	To include the extension study.
5.1.2	Subject Inclusion Criteria	Updated Inclusion Criterion #15 to reflect no contraceptive requirement for pembrolizumab and 90 days for docetaxel for males. In Inclusion Criteria #14 and #15, cross-references to the contraception guidance redirected to Section 12.8.	To reflect current contraceptive requirements.
5.1.3	Subject Exclusion Criteria	Removed Exclusion Criterion #19.	Redundant with language available elsewhere in the protocol.

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
5.7.2	Contraception	Deleted.	Not in the updated template. Redundant with language available elsewhere in the protocol.
5.7.4	Use in Nursing Mothers	Deleted.	Not in the updated template. Redundant with language available elsewhere in the protocol.
5.10	Beginning and End of the Trial	Added: Upon study completion, subjects are discontinued and may be enrolled in a pembrolizumab extension study, if available.	To include the extension study.
5.2.1.2	Dose Modification (Escalation/Titration/Other)	In table of dose modification and toxicity management guidelines for immune-related AEs associated with pembrolizumab: Added dose modification and toxicity management guidelines for neurological toxicities and exfoliative dermatologic conditions. Modified guidelines for pneumonitis, diarrhea/colitis, myocarditis, and other immune-related AEs.	To be aligned with current pembrolizumab package insert.

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
5.6.1	Supportive Care Guidelines	Added guidance for the use of epinephrine in table for pembrolizumab (MK-3475) infusion reaction dose modification and treatment guidelines.	To be aligned with current pembrolizumab package insert.
12.8	Contraception Guidance	Added.	To reflect current guidance.

ADDITIONAL CHANGE(S) FOR THIS AMENDMENT:

No additional changes.

1.0 TRIAL SUMMARY

Abbreviated Title	Pembrolizumab versus Docetaxel in second line NSCLC
Trial Phase	Phase III
Clinical Indication	The treatment of subjects with non-small cell lung cancer (NSCLC) whose tumors are positive for PD-L1 expression who have experienced disease progression after a platinum-containing systemic therapy
Trial Type	Interventional
Type of control	Active Control without Placebo
Route of administration	Intravenous
Trial Blinding	Unblinded Open-label
Treatment Groups	Pembrolizumab (MK-3475): 2 mg/kg every three weeks (Q3W) Docetaxel: 75 mg/m^2 Q3W
Number of trial subjects	Approximately 400 subjects will be enrolled.
Estimated duration of trial	The sponsor estimates that the trial will require approximately 4 years from the time the first subject signs the informed consent until the last subject's last study-related phone call or visit.
Duration of Participation	Each subject will participate in the trial from the time the subject signs the Informed Consent Form (ICF) through the final contact. After a screening phase of up to 42 days, eligible subjects will receive assigned treatment on Day 1 of each 3-week dosing cycle. Treatment with pembrolizumab (MK-3475) will continue until two years of delivery of pembrolizumab (MK-3475) every 3 weeks and no documented progression of disease, or 35 administrations of study medication, whichever is later, documented disease progression, unacceptable adverse event(s), intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw the subject, subject withdraws consent, pregnancy of the subject, noncompliance with trial treatment or procedure requirements, or administrative reasons. Pembrolizumab (MK-3475) treated subjects who attain complete response (CR) per Immune-Related Response Criteria (irRECIST) may be considered for stopping trial treatment. These subjects, as well as those subjects assigned to the pembrolizumab arm that stop trial therapy after 35 treatment administrations for reasons other than disease progression or intolerability, may be eligible for re-treatment with pembrolizumab for up to 17 administrations (12 months) in the Second Course Phase after they have experienced radiographic disease progression at the discretion of the investigator according to the criteria in Section 7.1.5.4. 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 unless the subject starts a new anticancer therapy between days 31 and 90). Subjects who have discontinued study treatment without confirmed disease progression will have post-treatment follow-up for disease status until initiating a non-study cancer treatment, experiencing disease progression, death, withdrawing consent, or becoming lost to follow-up whichever occurs first. Once the subject has achieved the study objective or the study has ended, the subject is discontinued from the study and may be enrolled in an extension study to continue protocol-defined assessments and treatment.
Randomization Ratio	1: 1

2.0 TRIAL DESIGN

2.1 Trial Design

This is a multi-country, multi-center, randomized, open-label, Phase III trial of intravenous (IV) pembrolizumab (MK-3475) versus docetaxel in subjects with NSCLC with programmed cell death ligand 1 (PD-L1) positive tumors who have experienced disease progression after platinum-containing systemic therapy. Approximately 400 PD-L1 positive subjects (defined as tumor proportion score (TPS) ≥1%) will be enrolled in this trial to examine the efficacy of pembrolizumab (MK-3475) compared to docetaxel in a population enriched for PD-L1 positive expression. The enrollment will continue until approximately 216 subjects with TPS ≥50% are randomized into pembrolizumab (MK-3475) arm and docetaxel arm. Subjects will be randomized in a 1:1 ratio to receive pembrolizumab (MK-3475) 2 mg/kg Q3W or docetaxel at 75 mg/m2 every 3 weeks (Q3W) (Figure 1). Randomization to pembrolizumab (MK-3475) or docetaxel will be unblinded, that is, the investigator and subjects will know the treatment administered. Subjects will be stratified by extent of tumoral PD-L1 expression (TPS 1-49% vs. TPS ≥50%).

Subjects will be evaluated every 9 weeks (63 ± 7 days) with radiographic imaging to assess response to treatment. Investigators will make all treatment-based decisions using Immune-Related Response Criteria (irRECIST) for subject receive pembrolizumab. Images will be assessed using Response Evaluation Criteria In Solid Tumors 1.1 (RECIST 1.1) for determination of objective response rate (ORR) and Progression-Free Survival (PFS). Adverse events (AEs) 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 pembrolizumab (MK-3475) will continue until two years of delivery of pembrolizumab (MK-3475) every 3 weeks and no documented progression of disease, or 35 administrations of study medication, whichever is later, documented disease progression, unacceptable adverse event(s), intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw the subject, subject withdraws consent, pregnancy of the subject, noncompliance with trial treatment or procedure requirements, or administrative reasons. Pembrolizumab (MK-3475) treated subjects who attain an investigator-determined confirmed complete response (CR) per Immune-Related Response Criteria in Solid Tumor (irRECIST) may consider stopping trial treatment. These subjects, as well as those subjects assigned to the pembrolizumab arm that stop trial therapy after 35 treatment administrations for reasons other than disease progression or intolerability, may be eligible for re-treatment with open-label pembrolizumab monotherapy after they have experienced radiographic disease progression at the discretion of the investigator according to defined criteria in Section 7.1.5.4. This re-treatment will be the Second Course Phase. Response or progression in the Second Course Phase will not count towards the ORR and PFS endpoints in this trial.

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 unless the subject starts a new anticancer therapy between days 31 and 90). Subjects who have discontinued study treatment without confirmed disease progression will have post-treatment follow-up for disease status until initiating a non-study cancer treatment,

experiencing disease progression, death, withdrawing consent, or becoming lost to follow-up whichever occurs first. In these subjects, the imaging evaluation will continue as scheduled.

Patients in the docetaxel group will not be allowed to cross over to MK-3475. Subjects in the Docetaxel arm may switch to another anti PD-1 treatment following the verification of progressive disease by blinded central radiologists' review.

The primary objectives of the trial are provided in Section 3.1. Refer to Section 7.1.4.4 for the requirement of tissue collection.

This trial will use an independent, external Data Monitoring Committee (eDMC) to monitor safety and efficacy. Detail of eDMC is provided in Section 7.3.2.

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.

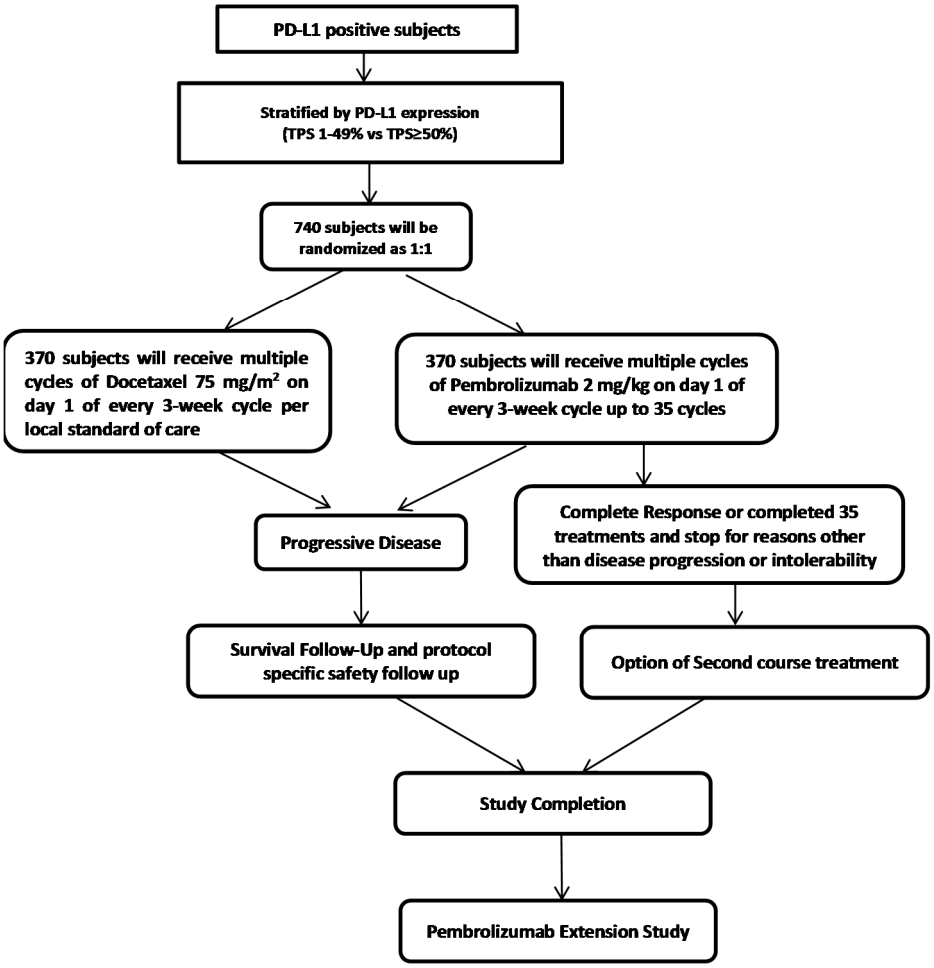

Figure 1 Trial Design

3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

3.1 Primary Objective(s) & Hypothesis(es)

In subjects with NSCLC whose tumors are positive (TPS ≥1%) for PD-L1 expression and have experienced disease progression after at least one platinum-containing systemic therapy.

(1) **Objective:** To evaluate OS in the TPS ≥50% stratum treated with pembrolizumab (MK-3475) compared to docetaxel.

Hypothesis: Pembrolizumab (MK-3475) prolongs OS in TPS ≥50% stratum compared to docetaxel.

(2) **Objective:** To evaluate OS in the TPS ≥1% population treated with pembrolizumab (MK-3475) compared to docetaxel.

Hypothesis: Pembrolizumab (MK-3475) prolongs OS in TPS ≥1% population compared to docetaxel.

(3) **Objective:** To evaluate PFS per RECIST 1.1 by blinded central radiologists' review in the TPS ≥50% stratum treated with pembrolizumab (MK-3475) compared to docetaxel.

Hypothesis: Pembrolizumab (MK-3475) prolongs PFS per RECIST 1.1 by blinded central radiologists' review in the TPS ≥50% stratum compared to docetaxel.

(4) **Objective:** To evaluate PFS per RECIST 1.1 by blinded central radiologists' review in the TPS ≥1% population treated with pembrolizumab (MK-3475) compared to docetaxel.

Hypothesis: Pembrolizumab (MK-3475) prolongs PFS per RECIST 1.1 by blinded central radiologists' review in the TPS ≥1% population compared to docetaxel.

The study is considered to have met its primary objective if pembrolizumab (MK-3475) is superior to docetaxel in OS at the interim or final analysis in the TPS ≥50% stratum.

3.2 Secondary Objective(s) & Hypothesis(es)

In subjects with NSCLC whose tumors are positive (TPS ≥1%) for PD-L1 expression and have experienced disease progression after at least one platinum-containing systemic therapy.

(1) **Objective:** To evaluate safety and tolerability profile of pembrolizumab (MK-3475) in subjects whose tumors are TPS ≥ 1%.

(2) **Objective:** To evaluate ORR and Duration of Response (DOR) per RECIST 1.1 by blinded central radiologists' review in the TPS ≥50% stratum and in the TPS ≥1% population treated with pembrolizumab (MK-3475) compared to docetaxel.

3.3 Exploratory Objectives

In subjects with NSCLC whose tumors are positive (TPS ≥1%) for PD-L1 expression and have experienced disease progression after at least one platinum-containing systemic therapy.

(1) **Objective:** To evaluate PFS, ORR and DOR per irRECIST by blinded central radiologists' review in subjects whose tumors have TPS ≥ 50% treated with pembrolizumab (MK-3475) compared to docetaxel.

(2) **Objective:** To evaluate changes in health-related quality-of-life assessments from baseline in subjects in the TPS ≥50% stratum treated with pembrolizumab (MK-3475) compared to docetaxel using the EORTC QLQ C-30 and EORTC QLQ LC-13.

(3) **Objective:** To characterize utilities in subjects in the TPS ≥ 50% stratum treated with pembrolizumab (MK-3475) compared to docetaxel using the EuroQoL EQ-5D.

4.0 BACKGROUND & RATIONALE

4.1 Background

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

4.1.1 Pharmaceutical and Therapeutic Background

The programmed cell death 1 (PD-1) pathway represents a major immune control switch which may be engaged by tumor cells to overcome active T-cell immune surveillance. The normal function of PD-1, expressed on the cell surface of activated T cells, under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions [1-4]. PD-1 is an immunoglobulin (Ig) superfamily member which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) [5; 6]. PD-L1 and PD-L2 are constitutively expressed at low levels in healthy organs, or can be induced in various tumors. High levels of expression of PD-L1 on tumor cells (and to a lesser extent of PD-L2) has been found to correlate with poor prognosis and poor survival in various cancer types, including renal cell carcinoma (RCC) [7], pancreatic carcinoma [8], hepatocellular carcinoma [9], ovarian carcinoma [10] and NSCLC.

The observed correlation of clinical prognosis with PD-L1 expression in multiple cancers suggests that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention. Therapeutic studies in mouse models have shown that administration of antibodies blocking PD-1/PD-L1 interaction enhances infiltration of tumor-specific CD8+ T-cells and leads ultimately to tumor rejection, either as a mono-therapy or in combination with other treatment modalities [8; 11-15]. Monoclonal antibodies (mAb) against PD-1 such as Nivolumab [16] (BMS-936558, MDX-1106) have been tested in multiple human solid tumors and promising clinical activity was noted in melanoma, renal cell carcinoma (RCC), and NSCLC at multiple doses up to 10 mg/kg Q2W. Nivolumab was also well tolerated up to the dose of 20 mg/kg in a phase I study in Japanese subjects with advanced solid tumors, and showed anti-tumor activities in melanoma, colorectal cancer (CRC), and thyroid carcinoma.

Pembrolizumab (MK-3475) is a potent and highly selective humanized monoclonal anti-PD-1 mAb of the IgG4/kappa isotype designed to directly block the interaction between PD-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 detailed information on pembrolizumab (MK-3475) is described in the IB.

Lung cancer is the most commonly diagnosed cancer and the leading cause of cancer death worldwide including China. NSCLC accounts for approximately 85% of all lung cancers. The mortality of NSCLC is much higher in China than in US and Europe. In China, age-

standardized incidence rate is 33.5 per 100,000 persons, with an estimated number of 522,050 patients per year. The age-standardized mortality rate is 28.7 per 100,000 persons, with an estimated number of 452,813 patients per year. Males have remarkably higher incidence and mortality than females. Lung cancer happens more frequently among people older than 45 year old, particularly in males. The incidence and mortality of lung cancer in China is expected to gradually increase in the next 20 years, attributed to cigarette smoking and air pollution [17; 18].

Per the National Comprehensive Cancer Network (NCCN) guideline, a systemic treatment for advanced or metastatic NSCLC is based on the histologic type, biomarker expression, performance status (PS) and previous treatment. Patients with advanced or metastatic NSCLC with EGFR wild type and no *echinoderm microtubule-associated protein-like 4* (*EML4*) gene is fused to the *muted lymphoma kinase* (*ALK*) gene (EML4-ALK) translocation are often treated with platinum-containing doublet chemotherapy as 1st line therapy. NSCLC with EGFR mutation or EML4-ALK positive are usually treated with tyrosine kinase inhibitors (TKIs) or Crizotinib. However, disease progression usually happens after the first line treatment and most of the patients require second line therapy. Median overall survival for patients treated with second-line chemotherapy is around 7.5 months [19-21]. So advances in the treatment of patients with NSCLC requiring second-line therapy are badly needed.

4.1.2 Ongoing Clinical Trials

Ongoing clinical trials are being conducted in advanced melanoma, non-small cell lung cancer, a number of advanced solid tumor indications and hematologic malignancies. In KN010, of the 2222 patients whose tumor samples were assessable for PD-L1 expression, 1475 (66%) had PD-L1 expression on at least 1% of tumor cells, including 633 (28%) with PD-L1 expression on at least 50% of tumor cells. For study details please refer to the IB.

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

Four second line chemotherapy products (docetaxel, pemetrexed, erlotinib, and gefitinib) have been approved for treatment of NSCLC in China. Pemetrexed's approved indication is limited to patients with NSCLC with non-squamous histology. Erlotinib and Gefitinib are inappropriate second-line therapy for patients with a good performance status who do not have an EGFR mutation. Docetaxel is a widely used and accepted second-line standard of care for patients with various histologic types of NSCLC, however the objective response rate is only about 5-10%, median progression-free survival is about 3 months, and the median overall survival is about 7.5 months [8; 19]. Improvements in OS are desirable since no one with progressive NSCLC is cured.

Proof of concept by targeting PD-1 pathway as a promising therapy for NSCLC has been achieved with two different anti-PD1 antibodies. The Phase I trial of anti-PD-1 antibody Nivolumab demonstrated that subjects with tumors expressing PD-L1 were more likely to respond to anti-PD-1 therapy than subjects with tumors that did not express PD-L1 [22]. Preliminary data from pembrolizumab (MK-3475) PN001 Part C also suggested that NSCLC subjects with high level of PD-L1 expression on their tumor are more likely to respond. The

activity of pembrolizumab (MK-3475) against NSCLC in patients from China and other countries will be confirmed in this proposed study.

Therefore, this study will compare monotherapy pembrolizumab (MK-3475) with standard of care docetaxel in subjects with NSCLC whose tumors exhibit PD-L1 expression. The patient's tumor will be classified as TPS ≥50% and TPS 1-49% based on PD-L1 scoring. OS and PFS in the TPS ≥50% and TPS≥1% subpopulation are the primary endpoints of this trial.

4.2.2 Rationale for Dose Selection/Regimen/Modification

An open-label Phase I trial (KEYNOTE 001) is being conducted to evaluate the safety and clinical activity of single agent pembrolizumab (MK-3475). The dose escalation portion of this trial evaluated three dose levels, 1 mg/kg, 3 mg/kg, and 10 mg/kg, administered every 2 weeks (Q2W) in subjects with advanced solid tumors. All three dose levels were well tolerated and no dose-limiting toxicities were observed. This first in human study of pembrolizumab (MK-3475) showed evidence of target engagement and objective evidence of tumor size reduction at all dose levels (1 mg/kg, 3 mg/kg and 10 mg/kg Q2W). No MTD has been identified.

In KEYNOTE 001, two randomized cohort evaluations of melanoma subjects receiving pembrolizumab (MK-3475) at a dose of 2 mg/kg versus 10 mg/kg Q3W have been completed, and one randomized cohort evaluating of 10 mg/kg Q3W versus 10 mg/kg Q2W has also been completed. The clinical efficacy and safety data demonstrate a lack of clinically important differences in efficacy response or safety profile at these doses. For example, in Cohort B2, advanced melanoma subjects who had received prior ipilimumab therapy were randomized to receive pembrolizumab (MK-3475) at 2 mg/kg versus 10 mg/kg Q3W. The ORR was 26% (21/81) in the 2mg/kg group and 26% (20/76) in the 10 mg/kg group (FAS). The proportion of subjects with drug-related AE, grade 3-5 drug-related AE, serious drug-related AE, death or discontinuation due to an AE was comparable between groups or lower in the 10 mg/kg group. In Cohort B3, advanced melanoma subjects (irrespective of prior ipilimumab therapy) were randomized to receive pembrolizumab (MK-3475) at 10 mg/kg Q2W versus 10 mg/kg Q3W. The ORR was 30.9% (38/123) in the 10mg/kg Q2W group and 24.8% (30/121) in the 10 mg/kg Q3W group (APaT). The proportion of subjects with drug-related AE, grade 3-5 drug-related AE, serious drug-related AE, death or discontinuation due to an AE was comparable between groups.

PK data analysis of pembrolizumab (MK-3475) administered Q2W and Q3W showed slow systemic clearance, limited volume of distribution, and a long half-life (refer to IB). Pharmacodynamic data (Interleukin 2 (IL-2) release assay) suggested that peripheral target engagement is durable (>21 days). This early PK and pharmacodynamic data provides scientific rationale for testing a Q3W dosing schedule. In addition to the pharmacodynamics data, Q3W dosing is more convenient for patients. Accordingly, Q3W dosing will be further studied.

The rationale for further exploration of 2 mg/kg and comparable doses of pembrolizumab (MK-3475) in solid tumors is based on the following: 1) similar efficacy and safety of pembrolizumab (MK-3475) when dosed at either 2 mg/kg or 10 mg/kg Q3W in melanoma patients, 2) the flat exposure-response relationships of pembrolizumab (MK-3475) for both efficacy and safety in the dose ranges of 2 mg/kg Q3W to 10 mg/kg Q3W, 3) the lack of

effect of tumor burden or indication on distribution behavior of pembrolizumab (MK-3475) (as assessed by the population PK model) and 4) the assumption that the dynamics of pembrolizumab (MK-3475) target engagement will not vary meaningfully with tumor type.

4.2.3 Rationale for Endpoints

4.2.3.1 Efficacy Endpoints

OS and PFS are the primary endpoints of the trial. PFS is an acceptable scientific endpoint for a randomized Phase III trial to demonstrate superiority of a new antineoplastic therapy, especially if it is believed that the median time to OS with the new therapy may be significantly longer than that seen with standard of care. OS is the gold standard endpoint to demonstrate superiority of antineoplastic therapy, but it is potentially impacted by other follow-up therapies such as cross-over for treatment failure. RECIST 1.1 will be used to determine progression as this methodology is accepted by regulatory authorities. Because the treatment assignment is unblinded regarding pembrolizumab (MK-3475) vs. docetaxel, images used for efficacy assessment will be read by independent radiologists blinded to treatment assignment to minimize bias in the response assessments. In addition, final determination of radiologic progression will be based on the central assessment of progression, rather than site assessment. Real-time determination of radiologic progression as determined by central review (verification of progressive disease (PD)) will be communicated to the site.

4.2.3.2 Safety Endpoints

The acceptable safety and tolerability of pembrolizumab (MK-3475) have been characterized in previous clinical studies among various solid tumors including NSCLC. This study will confirm the safety and tolerability of pembrolizumab (MK-3475) in previously-treated subjects with NSCLC in Asians with majority of subjects from China.

4.2.3.3 Immune-related RECIST

RECIST 1.1 will be adapted to account for the unique tumor response characteristics seen with treatment of pembrolizumab (MK-3475). Immunotherapeutic agents such as pembrolizumab (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. Such response patterns are referred to as pseudoprogression of the tumor. Standard RECIST 1.1 may, thus, not provide an accurate response assessment of immunotherapeutic agents such as pembrolizumab (MK-3475).

Based on an analysis of patients with melanoma enrolled in Keynote-001, 7 % of evaluable patients experienced delayed or early tumor pseudoprogression. Of note, patients who had progressive disease by RECIST 1.1 but not by immune related Response Criteria had longer OS than patients with progressive disease by both criteria. This data suggest that RECIST 1.1 may underestimate the benefit of pembrolizumab (MK-3475) in approximately 15% of patients. These findings support the need to apply a modification to RECIST 1.1 that takes

into account the unique patterns of atypical response in immunotherapy and enable treatment beyond initial radiographic progression.

Immune-related RECIST (irRECIST) is RECIST 1.1 adapted to account for the unique tumor response seen with immuno-therapeutics as described in Nishino et al., CCR 2013. The assessment of unidimensional target lesions and response categories per irRECIST are identical to RECIST 1.1. However, Merck has implemented an adaptation related to new lesions, non-target and tumor burden assessment in order to confirm radiographic progression. irRECIST will be used by local site investigators to assess tumor response and progression, and to make treatment decisions, as well as by the central imaging vendor in support of PFS as exploratory endpoint.

4.2.3.4 Patient Reported Outcome

EORTC QLQ-C30 and EORTC QLQ-LC13

The EORTC QLQ-C30 is the most widely used cancer specific Health-Related Quality of Life (HRQOL) instrument, which contains 30 items and measures five functional dimensions (physical, role, emotional, cognitive, and social), three symptom items (fatigue, nausea/vomiting, and pain), six single items (dyspnea, sleep disturbance, appetite loss, constipation, diarrhea, and financial impact), and a global health and quality of life scale [23]. This instrument is translated and validated into more than 80 languages. In addition to EORTC QLQ-C30, the EORTC QLQ-LC13 measures lung cancer associated symptoms (cough, hemoptysis, dyspnea, and site-specific pain), and treatment related symptoms (sore mouth, dysphagia, peripheral neuropathy, and alopecia) [24]. The EORTC QLQ-C30 and QLQ-LC13 are the most frequently utilized and reported patient reported outcome measures in lung cancer clinical trials [25; 26]. The reliability, validity and practicality of these instruments have been reported [24; 27].

EuroQol EQ-5D

The EuroQol-5D (EQ-5D) is a standardized instrument for use as a measure of health outcome. The EQ-5D will provide data for use in economic models and analyses including developing health utilities or quality-adjusted life-years (QALYs). The five health state dimensions in this instrument include the following: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension is rated on a three point scale from 1 (extreme problem) to 3 (no problem). The EQ-5D also includes a graded (0 to 100) vertical visual analog scale on which the patient rates his or her general state of health at the time of the assessment. The EQ-5D will always be completed by patients first before completing the EORTC QLQ C-30 and EORTC LC-13.

4.2.3.5 Future Biomedical Research

The Sponsor will conduct Future Biomedical Research on specimens collected for future biomedical research 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.

4.3 Benefit/Risk

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

Specific benefits to patients participating in the trial, (assuming that pembrolizumab (MK-3475)'s clinical activity in patients with previously-treated NSCLC is confirmed with this study), a patient has a 50% likelihood of being assigned Pembrolizumab (MK-3475). Patients in the TPS ≥50% subset who receive pembrolizumab (MK-3475) may be likely to experience a decrease in the size of their tumor burden, a longer time to progression of disease, and a longer survival relative to those who receive docetaxel. Risks to patients in this study relative to most others include the risk of pneumothorax, bleeding, and, rarely, death from a new tumor biopsy. Patients assigned to pembrolizumab (MK-3475) may be less likely to experience drug-related grade 3-4 toxicity, relative to docetaxel, but the development of autoimmune –mediated adverse events, including colitis, hyperthyroidism, hypothyroidism, and pneumonitis are possible.

While these autoimmune –mediated adverse events usually are manageable with hormone replacement and glucocorticoids, some cases may involve challenging management. Many thoracic oncologists are learning how to manage toxicities that may evolve from an activated immune system and most are not as comfortable managing adverse events from Pembrolizumab (MK-3475) as they might be from docetaxel. Considering all the factors, the benefit:risk profile for the study favors conducting the trial.

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

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

Male/Female subjects with NSCLC whose tumors are positive (TPS ≥1%) for PD-L1 expression and have experienced disease progression after at least one platinum-containing systemic therapy 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.

   Note: 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 ≥18 years of age on day of signing informed consent.
3. Chinese subject must be born, raised and reside within China.
4. Have a life expectancy of at least 3 months.
5. Have a histologically or cytologically confirmed diagnosis of stage IIIB/IV or recurrent NSCLC and have at least one measurable lesion as defined by RECIST 1.1.
6. Have investigator determined progression of disease per RECIST 1.1 after treatment with at least two cycles of a platinum-containing doublet, assessed from at least 2 dates of pre-trial images with diagnostic quality.

   Note: A platinum-containing doublet is defined as a platinum-based cytotoxic systemic agent administered in the same cycle as another cytotoxic systemic chemotherapeutic agent. Completion of treatment with a platinum-containing doublet as adjuvant therapy within one year of signing informed consent will satisfy the prior treatment requirement.

7. Site must be able to provide documentation of EGRF mutation and ALK translocation status. If the site is unable to provide this source documentation, then the Sponsor will offer this molecular testing of the tumor. Subjects will not be randomized until EGFR mutation and ALK translocation status is available in source documentation at the site with the exceptions noted in sub-bullet c and d below:

   a. Subjects with an EGFR sensitizing mutation tumor will be excluded.

   b. Subjects with an ALK translocation must be able to demonstrate progression of disease on both platinum-containing doublet and ALK-directed tyrosine kinase inhibitor (examples: crizotinib, ceritinib, alectinib etc.). Radiographic images that demonstrate progression after initiation of the ALK-directed tyrosine kinase inhibitor therapy and platinum-containing doublet or combination of ALK-directed tyrosine kinase inhibitor and platinum-containing doublet as first line therapy must be submitted prior to randomization. An exception is the subject who receives four cycles of a platinum doublet does not experience progression of disease, and begins

ALK-directed tyrosine kinase inhibitor as a maintenance therapy within 28 days of the last administration of the platinum doublet chemotherapy. For this subject, only one set of images demonstrating progression on the ALK-directed tyrosine kinase inhibitor is required for submission for the subject to be eligible.

c. If a patient is known to have one molecular alteration (either sensitizing EGFR mutation or ALK translocation), then testing for the other alteration is not required.

d. For patients enrolled who are known to have a tumor with pure squamous histology, molecular testing for EGFR mutation and ALK translocation will not be required as this is not standard of care and is not part of current diagnostic guidelines. Patients with adenosquamous histology or any component of adenocarcinoma in mixed histology are required to have EGFR testing done.

8. Have a performance status of 0 or 1 on the ECOG Performance Scale as assessed within 10 days prior to randomization.

9. Have adequate organ function as indicated in Table 1 below:

Table 1 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1,500 /mcL
Platelets	≥100,000 / mcL
Hemoglobin	≥9 g/dL or ≥5.6 mmol/L without transfusion for 4 weeks
Renal	
Serum creatinine **OR** Measured or calculated[a] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5xULN OR ≥60 mL/min for subject with creatinine levels >1.5x institutional ULN
Hepatic	
Serum total bilirubin	≤1.5xULN **OR** Direct bilirubin ≤ULN for subjects with total bilirubin levels >1.5xULN
AST (SGOT) and ALT (SGPT)	≤1.5xULN
Alkaline Phosphatase	≤ 2.5 X ULN
Endocrine	
Thyroid stimulating hormone (TSH)[b]	Within normal limits
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT)	≤1.5xULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
Activated Partial Thromboplastin Time (aPTT)	≤1.5xULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants

[a] Creatinine clearance should be calculated per institutional standard. 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)
[b] If TSH is not within normal limits at baseline, the subject may still be eligible if T3/FT3 and free T4 are within the normal limits.

10. Have provided archival tumor tissue sample or newly obtained formalin fixed tumor tissue from a recent biopsy of a tumor lesion not previously irradiated.

    Note: The investigator may submit an archival formalin-fixed, paraffin embedded tumor specimen for PD-L1 analysis**.** The tissue sample must be received and evaluated by the central vendor prior to randomization. Fine needle aspirates are not acceptable. Core needle or excisional biopsies, or resected tissue is required.

11. Have a PD-L1 positive tumor as determined by immunohistochemistry (IHC) at a central laboratory.

    Note: Only PD-L1 positive patients will be randomized. If a patient's initial tumor specimen is not classified as PD-L1 positive by the central laboratory, a newly obtained specimen (different from the sample previously submitted) may be submitted for testing. If the newer specimen is classified as PD-L1 positive by the central laboratory, the patient meets this eligibility criterion.

12. Have resolution of toxic effect(s) of the most recent prior chemotherapy to Grade 1 or less (except alopecia). If subject received major surgery or radiation therapy of > 30 Gy, they must have recovered from the toxicity and/or complications from the intervention.

13. Female subjects of childbearing potential must 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 cannot be confirmed as negative, a serum pregnancy test will be required.

14. Female subjects of childbearing potential (Section 12.8) must be willing to use an adequate method of contraception as outlined in Section 12.8 – Contraceptive Guidance, for the course of the study through 120 days after the last dose of pembrolizumab (MK-3475) or 180 days after the last dose of docetaxel.

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

15. Male subjects of childbearing potential must agree to use an adequate method of contraception as outlined in Section 12.8- Contraceptive Guidance, starting with the first dose of study therapy through 90 days after the last dose of docetaxel.

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

5.1.3 Subject Exclusion Criteria

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

1. Has received prior therapy with docetaxel for NSCLC.
2. Is currently participating or has participated in a study of an investigational agent or has used an investigational device within 4 weeks prior to the first dose of trial treatment.

   Note: Subjects who have entered the follow-up phase of an investigational trial may participate as long as it has been 4 weeks after the last dose of the previous investigational agent.

3. Is receiving systemic steroid therapy within three days prior to the first dose of trial treatment or receiving any other form of immunosuppressive medication (corticosteroid use on study for management of ECIs or as a pre-medication for docetaxel is allowed).
4. Is expected to require any other form of systemic or localized antineoplastic therapy while on trial (including maintenance therapy with another agent for NSCLC or radiation therapy).

   Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed after consultation with Sponsor.
5. Has received prior systemic cytotoxic chemotherapy, antineoplastic biological therapy (e.g., cetuximab), any other agents used as systemic treatment for cancer, or major surgery within 3 weeks of the first dose of trial treatment; received thoracic radiation therapy of > 30 Gy within 6 months of the first dose of trial treatment; received prior ALK-directed tyrosine kinase inhibitor therapy or completed palliative radiotherapy of 30 Gy or less within 7 days of the first dose of trial treatment.
6. Has received prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, with an agent directed to an agonist or antagonist T-cell check point receptor (i.e., CTLA-4, OX-40, CD137), or has previously participated in Merck sponsored clinical trials evaluating pembrolizumab (MK-3475).
7. Has a known additional malignancy that is progressing or requires active treatment. Exceptions include early stage cancers (carcinoma in situ or Stage 1) treated with curative intent, basal cell carcinoma of the skin, squamous cell carcinoma of the skin, in situ cervical cancer, or in situ breast cancer that has undergone potentially curative therapy.
8. Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by MRI for at least four weeks prior to the first dose of trial treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are using no steroids for at least three days prior to study medication.
9. Has active autoimmune disease that has required systemic treatment in past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.
10. Has had an allogeneic tissue/solid organ transplant.
11. Has a history of (non-infectious) pneumonitis that required steroids or current pneumonitis.
12. Has received or will receive a live vaccine within 30 days prior to the first administration of study medication. Seasonal flu vaccines that do not contain live virus are permitted.
13. Has an active infection requiring intravenous systemic therapy.
14. Has known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).

15. Has known active Hepatitis B or C. Active Hepatitis B is defined as a known positive HBsAg result. Active Hepatitis C is defined by a known positive Hep C Ab result and known quantitative HCV RNA results greater than the lower limits of detection of the assay.
16. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.
17. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.
18. Is, at the time of signing informed consent, a regular user (including "recreational use") of any illicit drugs or had a recent history (within the last year) of substance abuse (including alcohol).
19. Removed.
20. Require treatment with a strong inhibitor of CYP3A4 will be excluded. Subject may be included if there is an alternate treatment available (not a strong CYP3A4 inhibitor) and they are willing to switch prior to randomization. If a subject opts to change from a strong CYP 3A4 inhibitor to a weaker CYP 3A4 inhibitor, the subject must stop the strong CYP 3A4 inhibitor 7 days before study drug administration. Please refer to Section 5.5.2 for Prohibited Concomitant Medications.

5.2 Trial Treatment(s)

The treatments to be used in this trial are outlined below in Table 2.

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

Table 2 Trial Treatment

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/ Treatment Period	Use
Pembrolizumab (MK-3475)	2 mg/kg	Q3W	IV infusion	Day 1 of each cycle	Experimental
Docetaxel	75 mg/m^2	Q3W	IV infusion	Day 1 of each cycle	Experimental

All supplies indicated in Table 2 will be provided centrally by the Sponsor or locally by the trial site, subsidiary or designee, depending on local country operational or regulatory requirements.

The trial site will be responsible for recording the lot number, manufacturer and expiry date of any locally purchased 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 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 & Rationale.

The dose amount required to prepare the pembrolizumab (MK-3475) infusion solution will be based on the subject's weight in kilograms (kg). The details will be described in the Pharmacy Manual.

Docetaxel will be prepared and administered as per the approved product label.

5.2.1.2 Dose Modification (Escalation/Titration/Other)

Docetaxel

Refer to approved product label for subjects receiving docetaxel.

Pembrolizumab (MK-3475)

Adverse events associated with pembrolizumab exposure may represent an immune-related response. These irAEs may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab are provided in Table 3 below. See Section 5.6.1 for supportive care guidelines, including use of corticosteroids.

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

General instructions:

1. Severe and life-threatening irAEs should be treated with IV corticosteroids followed by oral steroids. Other immunosuppressive treatment should begin if the irAEs are not controlled by corticosteroids.
2. Study intervention must be permanently discontinued if the irAE does not resolve or the corticosteroid dose is not ≤10 mg/day within 12 weeks of the last study intervention treatment.
3. The corticosteroid taper should begin when the irAE is ≤ Grade 1 and continue at least 4 weeks.
4. If study intervention has been withheld, study intervention may resume after the irAE decreased to ≤ Grade 1 after corticosteroid taper.

Immune-related AEs	**Toxicity grade or conditions (CTCAEv4.0)**	**Action taken to pembrolizumab**	**Corticosteroid and/or other therapies**	**Monitor and follow-up**
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper • Add prophylactic antibiotics for opportunistic infections	• Monitor subjects for signs and symptoms of pneumonitis • Evaluate subjects with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor subjects for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus). • Subjects with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. • Subjects with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

Immune-related AEs	Toxicity grade or conditions (CTCAEv4.0)	Action taken to pembrolizumab	Corticosteroid and/or other therapies	Monitor and follow-up
AST / ALT elevation or Increased bilirubin	Grade 2[a]	Withhold	• Administer corticosteroids (initial dose of 0.5- 1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable
	Grade 3[b] or 4[c]	Permanently discontinue	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold[d]	• Initiate insulin replacement therapy for subjects with T1DM • Administer anti-hyperglycemic in subjects with hyperglycemia	• Monitor subjects for hyperglycemia or other signs and symptoms of diabetes.
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated.	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hypothyroidism	Grade 2, 3, or 4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care	• Monitor for signs and symptoms of thyroid disorders.

Immune-related AEs	Toxicity grade or conditions (CTCAEv4.0)	Action taken to pembrolizumab	Corticosteroid and/or other therapies	Monitor and follow-up
Nephritis: grading according to increased creatinine or acute kidney injury	Grade 2	Withhold	• Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper.	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Neurological Toxicities	Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 2, 3, or 4	Permanently discontinue		
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Confirmed SJS, TEN, or DRESS	Permanently discontinue		
All other immune-related AEs	persistent Grade 2	Withhold	• Based on type and severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3	Withhold or discontinue based on the type of event.[e]		
	Grade 4 or recurrent Grade 3	Permanently discontinue		

Immune-related AEs	Toxicity grade or conditions (CTCAEv4.0)	Action taken to pembrolizumab	Corticosteroid and/or other therapies	Monitor and follow-up

AE(s)=adverse event(s); ALT= alanine aminotransferase; AST=aspartate aminotransferase; CTCAE=Common Terminology Criteria for Adverse Events; DRESS=Drug Rash with Eosinophilia and Systemic Symptom; GI=gastrointestinal; IO=immuno-oncology; ir=immune related; IV=intravenous; SJS=Stevens-Johnson Syndrome; T1DM=type 1 diabetes mellitus; TEN=Toxic Epidermal Necrolysis; ULN=upper limit of normal.

Note: Non-irAE will be managed as appropriate, following clinical practice recommendations.

[a] AST/ALT: >3.0 to 5.0 x ULN if baseline normal; >3.0 to 5.0 x baseline, if baseline abnormal; bilirubin:>1.5 to 3.0 x ULN if baseline normal; >1.5 to 3.0 x baseline if baseline abnormal.

[b] AST/ALT: >5.0 to 20.0 x ULN, if baseline normal; >5.0 to 20.0 x baseline, if baseline abnormal; bilirubin:>3.0 to 10.0 x ULN if baseline normal; >3.0 to 10.0 x baseline if baseline abnormal.

[c] AST/ALT: >20.0 x ULN, if baseline normal; >20.0 x baseline, if baseline abnormal; bilirubin: >10.0 x ULN if baseline normal; >10.0 x baseline if baseline abnormal.

[d] The decision to withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician. If control achieved or ≤ Grade 2, pembrolizumab may be resumed.

[e] Events that require discontinuation include but are not limited to encephalitis and other clinically important irAEs.

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

Trial treatment should be administered on Day 1 of each cycle after all procedures/ assessments have been completed. Trial treatment may be administered up to 3 days after Day 1 of each cycle due to administrative reasons only.

Pembrolizumab (MK-3475) will be administered as a 30-minute IV infusion Q3W. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min).

The Procedures Manual contains specific instructions for pembrolizumab (MK-3475) dose calculation, reconstitution, preparation of the infusion fluid, and administration.

Docetaxel 75 mg/m^2 will be administered as an IV infusion over 1 hour every Q3W. All subjects should be pre-medicated with oral or injectable steroids according to the approved product label and/or standard practice. Additional pre-medications should be administered as per standard practice.

Investigators treating subjects, if clinically stable, assigned to docetaxel who experience disease progression may elect to interrupt treatment by deferring the decision to continue/discontinue treatment in the trial until confirmation of disease progression per irRECIST at least 28 days from the date of imaging demonstrating disease progression. Patients treated with docetaxel for whom disease progression is not confirmed on subsequent imaging may resume treatment with docetaxel.

5.2.3 Trial Blinding/Masking

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

Imaging data for the primary analysis will be centrally reviewed by independent radiologist(s) without knowledge of subject treatment assignment.

The sites will be notified the positive and negative PD_L1 results for enrollment but the details of PD_L1 score will not be shared with the sites and will be directly transferred to IVRS for stratification. The sites, the principal investigators, sub-investigators and their staff as well as Merck’s clinical research coordinators (CRAs) involved in on-site monitoring will remain blinded to the details of PD_L1 score.

5.3 Randomization or Treatment Allocation

Treatment allocation/randomization will occur centrally using an interactive voice response system / integrated web response system (IVRS/IWRS). There are 2 treatment arms. Subjects will be assigned randomly in a 1:1 ratio to pembrolizumab (MK-3475) 2 mg/kg Q3W, or docetaxel 75 mg/m^2 Q3W.

5.4 Stratification

Treatment allocation/randomization will be stratified according to the following factor:

- Extent of tumor PD-L1 expression (TPS ≥50% vs. TPS 1-49%)

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 Acceptable Concomitant Medications

All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with 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 will also be included on the CRF.

Specifically, subjects using bisphosphonates or anti-RANKL mAb who were receiving this medication prior to study start, may continue receiving the medication during the study.

All concomitant medications received within 30 days before the first dose of trial treatment through the Safety Follow-up Visit should be recorded. After the Safety Follow-up Visit record all medications taken 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, Treatment and Second Course Phases of this trial (unless otherwise noted below):

- Antineoplastic systemic chemotherapy or biological therapy not specified in this Protocol.
- Immunotherapy not specified in this protocol.
- Chemotherapy not specified in this protocol.
- Investigational agents other than pembrolizumab (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 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, seasonal flu, H1N1 flu, rabies, BCG, and typhoid vaccine. Seasonal flu vaccines that do not contain live viruses are permitted.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an immune-related adverse Event (as listed in Section 5.6) or for use as a pre-medication for chemotherapeutic agents specified in the protocol or as a pre-medication prior to a CT scan for subjects with contrast allergy or for use for COPD exacerbation requiring steroid for recovery. Replacement doses of steroids (for example, prednisone 10 mg daily) are permitted while on study.
- Strong inhibitors of the CYP3A4 enzymes (a common list of such agents may be found in Appendix 12.7).

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

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

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

5.6 Rescue Medications & Supportive Care

5.6.1 Supportive Care Guidelines

Docetaxel

Pre-medication(s) for docetaxel will be given as per standard of care. Corticosteroid Pretreatment and/or post treatment of docetaxel is acceptable in concordance with the local label or standard of care.

Pembrolizumab (MK-3475)

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 in Table 3. 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 (MK-3475).

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 5.2.1.2 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.

Signs and symptoms of infusion reactions usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion.

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

Table 4 Pembrolizumab (MK-3475) Infusion Reaction Dose Modification and Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the 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).

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
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: Epinephrine** IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids 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. **In cases of anaphylaxis, epinephrine should be used immediately. **Subject is permanently discontinued from further trial treatment administration.**	No subsequent dosing
h=hour; IV=intravenous; CTCAE=Common Terminology Criteria for Adverse Events; NCI=National Cancer Institute; NSAIDs= nonsteroidal anti-inflammatory drugs. Note: Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE) at http://ctep.cancer.gov		

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 Use in Pregnancy

If a female subject inadvertently becomes pregnant while on treatment with docetaxel or pembrolizumab (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. If a male subject impregnates his female partner the study

personnel at the site must be informed immediately and the pregnancy reported to the Sponsor and followed as described above and in Section 7.2.2.

5.8 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.

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

- Documented disease progression.

  Note: If a subject has confirmed progression of disease by irRECIST, the subject should not receive further trial treatment on study. If a subject has unconfirmed progression of disease and is clinically stable, it is at the discretion of the investigator to continue treating the subject with the assigned treatment per protocol until progression of disease is confirmed at least 28 days from the date of the scan suggesting progression of disease. Clinical Stability is defined as:

  - Absence of symptoms and signs indicating clinical significant progression of disease (including worsening of laboratory values) indicating disease progression.
  - No decline in ECOG performance status.
  - Absence of rapid progression of disease or progressive tumor at critical anatomical sites (e.g., cord compression) requiring urgent alternative medical intervention.
- Unacceptable adverse experiences as described in Section 5.2.1.2.
- Two years of delivery of pembrolizumab (MK-3475) every 3 weeks and no documented progression of disease, or 35 administrations of study medication, whichever is later. These patients may be eligible for re-treatment with open-label pembrolizumab monotherapy after they have experienced radiographic disease progression at the discretion of the investigator according to defined criteria in Section 7.1.5.4.
- Intercurrent illness that prevents further administration of treatment.
- Investigator's decision to discontinue the subject from treatment.
- The subject has a confirmed positive serum pregnancy test.

- Noncompliance with trial treatment or procedure requirements.
- Administrative reasons.
- If a pembrolizumab (MK-3475) treated subject attains an investigator-determined confirmed CR according to irRECIST, has been treated for at least six months with pembrolizumab (MK-3475), and has at least two treatments with pembrolizumab (MK-3475) beyond the date when the initial CR was declared, the subject and investigator may consider stopping therapy with pembrolizumab (MK-3475). Subjects who discontinue pembrolizumab and then experience radiographic disease progression by local investigator's assessment according to irRECIST may be eligible for re-treatment with pembrolizumab in the Second Course Phase at the discretion of the Investigator as described in Section 7.1.5.4.

The End of Treatment and Follow-up visit procedures are listed in Section 6 - Trial Flow Chart and Section 7.1.5 - Visit Requirements. 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 as described in Section 7.2.3.1). Subjects will have post-treatment follow-up for disease status until disease progression, initiating a non-study cancer treatment, withdrawing consent, or becoming lost to follow-up or entering the Second Course Phase.

- After documented disease progression each subject will be followed for overall survival until death or withdrawal of consent.

5.9 Subject Replacement Strategy

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

5.10 Beginning and End of the Trial

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

Upon study completion, subjects are discontinued and may be enrolled in a pembrolizumab extension study, if available.

5.11 Clinical Criteria for Early Trial Termination

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

1. The trial will be stopped early for efficacy at the recommendation of the eDMC if the interim analysis results show pembrolizumab (MK-3475) is superior to docetaxel in OS.
2. The trial will be stopped early at the recommendation of the eDMC if the risk/benefit ratio to the trial population as a whole is unacceptable.

Enrollment will not be halted during the planned interim analyses.

Further recruitment in the trial or at (a) particular trial site(s) may be stopped due to insufficient compliance with the protocol, GCP and/or other applicable regulatory requirements, procedure-related problems or the number of discontinuations for administrative reasons is too high.

5.12 Post Pembrolizumab (MK-3475)/Docetaxel Therapies

After a subject stops the designated study treatment for one of the reasons described in Section 5.8, other than for an irCR, the subject may be interested in pursuing other therapies. If investigators assess that the subject is fit for subsequent therapy, it is encouraged. The exact subsequent treatment(s) used will be at the discretion of the investigator and determined by the interests of the subject.

6.0 TRIAL FLOW CHART

6.1 Treatment Phase

Pembrolizumab (MK-3475) 2 mg/kg Q3W and Docetaxel 75 mg/m^2 Q3W

	Screening (Visit 1)	Treatment Cycles[1]														End of Treatment
Treatment Cycle / Scheduled Time	-42 to -1	1	2	3	4	5	6	7	8	9	10	11	12	13	14 and beyond	Discontinuation Visit
Scheduling Window (Days):[2]			±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	
Administrative Procedures																
Informed Consent [3]	X															
Informed Consent for Future Biomedical Research [4] (optional)	X															
Inclusion/Exclusion Criteria	X															
Subject Identification Card	X															
Demographics and Medical History	X															
Prior and Concomitant Medications[5]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
NSCLC Disease Details and Prior Treatment	X															
Trial Treatment Administration		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Assignment of Screening Number	X															
Survival Status[23]		<----------														---------->
Clinical Procedures / Assessments																
Review Adverse Events [6]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Full Physical Examination[18]	X															X[18]
Directed Physical Examination[18]		X	X	X		X	X		X	X		X	X		X[18]	X
Vital Signs and Height [7]	X[7]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-Lead ECG	X															
ECOG Performance Status	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

	Screening (Visit 1)	Treatment Cycles[1]														End of Treatment
Treatment Cycle / Scheduled Time	-42 to -1	1	2	3	4	5	6	7	8	9	10	11	12	13	14 and beyond	Discontinuation Visit
Scheduling Window (Days):[2]			±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	
Laboratory Procedures / Assessments: analysis performed by local laboratory																
Pregnancy Test - Urine or Serum β-HCG [8]	X															
PT/INR and aPTT [9]	X [10]															
CBC with Differential[11]	X [10]		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Comprehensive Serum Chemistry Panel[11,22]	X [10]		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis[11]	X [10]					X				X				X[12]		X
T3/FT3, FT4 and TSH [11, 12]	X [10]		X		X		X		X		X		X		X [12]	X
ALK Translocation Testing[19]	X															
EGFR Mutation Testing[19]	X															
HBsAg	X[22]															
Anti HCV	X[22]															
Laboratory Procedures / Assessments: analysis performed by central laboratory																
Blood for Future Biomedical Research[13] (optional)		X														
Tissue for PD-L1 status	X															
Efficacy Measurements																
Tumor Imaging [14, 15]	X				X			X			X			X	X[14]	X[21]
Patient Report Outcomes (PRO)																
EuroQoL EQ-5D [20]		X	X	X	X			X			X			X		X
EORTC QLQ-C30 [20]		X	X	X	X			X			X			X		X
EORTC QLQ-LC-13 [20]		X	X	X	X			X			X			X		X
Tumor Biopsies / Archival Tissue Collection																
Tumor Tissue Collection	X[16]			X[17]			X[17]			X[17]						

	Screening (Visit 1)	Treatment Cycles[1]													End of Treatment
Treatment Cycle / Scheduled Time	-42 to -1	1	2	3	4	5	6	7	8	9	10	11	12	13	14 and beyond	Discontinuation Visit
Scheduling Window (Days**):**[2]			±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	

1. In general, assessments/procedures are to be performed on Day 1 and prior to the first dose of trial treatment for each cycle unless otherwise specified. Treatment cycles are 3 weeks (21-days); however the pembrolizumab (MK-3475) treatment cycle interval may be increased due to toxicity according to the dose modification guidelines provided in Section 5.2.1. If treatment cycles are increased all procedures except imaging will be completed according to the Cycle number and not weeks on treatment, imaging will be performed every 9 weeks (± 7 days) from the date of randomization regardless of any treatment delays.
2. In general, the window for each visit is ± 3 days unless otherwise specified.
3. 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 42 days prior to the first dose of trial treatment). Assign Baseline number when the study informed consent is signed.
4. Signing the informed consent for future biomedical research (FBR) samples is optional. Informed consent for future biomedical research (FBR) must be obtained prior to sample collection. Detailed instructions for the collection and management of specimens for FBR are provided in the procedures manual and full protocol.
5. Prior medications - Record all medications taken within 30 days of start of treatment cycle 1 and all treatments for a prior cancer other than NSCLC even if taken greater than 30 days prior to first dose of trial treatment (prior treatments for NSCLC will be recorded separately). Concomitant Medications - Enter new medications started during the trial through the Safety Follow-up Visit. After the Safety Follow-up Visit record all medications taken for SAEs and ECIs as defined in full protocol.
6. AEs and laboratory safety measurements will be graded per NCI CTCAE version 4.0. All AEs, whether gradable by CTCAE or not, will also be evaluated for seriousness.
7. Vital signs to include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at Visit 1 only.
8. For women of reproductive potential, a urine pregnancy test will 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. Monthly pregnancy testing should be conducted as per local regulations where applicable.
9. Coagulation factors (PT/INR and aPTT) should be monitored closely throughout the trial for any subject receiving anticoagulant therapy.
10. Laboratory tests for screening are to be performed within 10 days prior to the first dose of trial treatment.
11. After Cycle 1, lab samples can be collected up to 72 hours prior to the scheduled time point. Laboratory results must be known and acceptable prior to dosing.
12. Urinalysis will be performed every 4 cycles after Cycle 13; perform thyroid testing every **other** cycle. Thyroid function tests will be performed by a central laboratory only if the local laboratory is unable to perform this service.
13. Informed consent for future biomedical research samples must be obtained before the DNA sample. DNA sample for analysis should be obtained predose, on Cycle 1 (or with the next scheduled blood draw), as the last sample drawn, on randomized subjects only, or at a later date as soon as the informed consent is obtained. Detailed instructions for the collection and management of specimens for FBR are provided in the Procedures manual and full protocol.
14. The initial tumor imaging will be performed within 28 days prior to the date of randomization. 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 28 days prior to the first dose of trial treatment. Local reading (investigator assessment with site radiology reading) will be used to determine eligibility and for subject management. The Sponsor will collect radiological assessments for analysis by a central imaging vendor. The processes for image collection and transmission to the central vendor are in the Site Imaging Manual.
15. After the first documentation of progression (if the subject is clinically stable) or response per irRECIST repeat imaging for confirmation is required. Confirmatory imaging may be performed as early as 28 days later; alternately, the scan performed at the next scheduled time point (e.g. every 63 ±7 days) may be used as confirmation.
16. Tumor tissue for biomarker analysis (archival tumor tissue sample or newly obtained formalin fixed tumor tissue from a resent biopsy of a tumor lesion not previously

	Screening (Visit 1)	Treatment Cycles[1]													End of Treatment
Treatment Cycle / Scheduled Time	-42 to -1	1	2	3	4	5	6	7	8	9	10	11	12	13	14 and beyond	Discontinuation Visit
Scheduling Window (Days**):**[2]			±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	

irradiated are required for PD-L1 determination) must be provided and received by the central vendor before randomization. For patients enrolled who are known to have a tumor with pure squamous histology, molecular testing for EGFR mutation and ALK translocation will not be required. Patients with adenosquamous histology or any component of adenocarcinoma in mixed histology are required to have EGFR testing done. 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 biopsies that would ordinarily be discarded at the end of the main study will be retained for FBR.

17. Pembrolizumab (MK-3475) treated subjects in the Treatment Phase – Additional optional biopsies at approximately Week 6, Week 12 and Week 24 and at disease progression are highly desired when feasible; these biopsies will only be performed in non-target lesions after disease progression has been confirmed. Detailed instructions for tissue collection, processing and shipment are provided in the Procedures Manual. **THESE SAMPLES ARE TO BE COLLECTED ONLY FROM NON-TARGET LESIONS, TO AVOID ANY IMPACT ON irRECIST OUTCOMES.** Additional biopsy samples at disease progression can be obtained from the target lesion, but only after confirmation of disease progression by the Central Imaging Vendor.
18. Perform a full physical examination at baseline and end of treatment and perform directed PE at other visits.
19. Site must be able to provide documentation of the subject's tumor EGFR mutation and ALK translocation status. If the site is unable to provide this source documentation, then the Sponsor will offer this molecular testing of the tumor.
20. Patient Reported Outcomes (PROs) are to be administered by trained site personnel and completed by subjects. It is strongly recommended that PROs are administered prior to drug administration, adverse event evaluation and disease status notification starting with the EQ-5D, followed by EORTC QLQ-C30, and EORTC LC-13; an exception to this recommendation may occur at the treatment discontinuation visit where patients may have already been notified of their disease status or an AE evaluation is known prior to them arriving to the clinic. All PROs are to be performed at Cycle 1, Cycle 2, Cycle 3, Cycle 4, and every 3 cycles (9 weeks) thereafter (e.g., Cycle 7, Cycle 10, Cycle 13, etc.) up to a year or End of Treatment, whichever comes first. If the subject does not complete the PROs, the MISS_MODE form must be completed to capture the reason the assessment was not performed.
21. In subjects who discontinue study therapy without centrally verified disease progression, a radiologic evaluation should be performed at the time of treatment discontinuation (i.e., date of discontinue ± 4 week window). If a previous scan was obtained within 4 weeks prior to the date of discontinuation, then a scan at treatment discontinuation isn't mandatory.
22. Tests will be performed by a central laboratory only if the local laboratory is unable to perform this service. The need for additional testing due to positive test results will be at the discretion of the Investigator.
23. After documented local site assessed disease progression, or the start of new anticancer treatment; contacts are approximately every 2 months by telephone. Updated survival status may be requested by the Sponsor at any time during the course of the study. Upon Sponsor notification, all subjects who do not/will not have a scheduled study visit or study contact during the Sponsor-defined time period will be contacted for their survival status (excluding subjects who have a death event previously recorded).

6.2 Post-Treatment Follow-Up Phase

Trial Phase	Safety Follow-up [1]	Follow-up [2]			Survival Follow-up[3]
Time from Last Dose of Trial Treatment	30 Days	3 Months	6 Months	Every 9 weeks (63 days) after Month 6	Approx. Every 2 Months
Visit	Safety Follow-up Visit	Follow-up Visit 1	Follow-up Visit 2	Follow-up Visit 3 and beyond	Survival Follow-up Visit 1 and beyond
Scheduling Window	+ 7 days	± 7 days	± 7 days	± 7 days	± 14 days
Administrative Procedures					
Review Medications	X				
Subsequent antineoplastic therapy Status	X	X	X	X	X
Survival Status [3]	<----------	----------	----------	---------->	X
Clinical Procedures/Assessments					
Review Adverse Events [4]	X	X	X	X	X
ECOG Performance Status	X	X	X		
Directed Physical Examination	X	X	X		
Vital Signs [5]	X	X	X		
Efficacy Measurement					
Tumor Imaging [6]	X[7]	X[7]	X[7]	X[7]	
Laboratory Procedures/Assessments: analysis performed by local laboratory					
CBC with Differential [8]	X				
Comprehensive Serum Chemistry Panel [8]	X				
T3/FT3, FT4 and TSH [9]	X				
Patient Report Outcomes (PRO)					
EuroQoL EQ-5D [10]	X				
EORTC QLQ-C30 [10]	X				
EORTC QLQ-LC-13 [10]	X				

Trial Phase	Safety Follow-up [1]	Follow-up [2]			Survival Follow-up[3]
Time from Last Dose of Trial Treatment	30 Days	3 Months	6 Months	Every 9 weeks (63 days) after Month 6	Approx. Every 2 Months
Visit	Safety Follow-up Visit	Follow-up Visit 1	Follow-up Visit 2	Follow-up Visit 3 and beyond	Survival Follow-up Visit 1 and beyond
Scheduling Window	+ 7 days	± 7 days	± 7 days	± 7 days	± 14 days

1. 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 antineoplastic treatment, whichever comes first. Subjects with an AE of Grade >1 will be further followed until the resolution of the AE to Grade 0-1 or until beginning of a new antineoplastic therapy, whichever occurs first.
2. Subjects who discontinue trial treatment for a reason other than disease progression will move into the Follow-up Phase and should be assessed every 9 weeks (63 ± 7 days) by radiologic imaging to monitor disease status. Follow-up Visit 1 should be scheduled 3 months after the last dose of trial treatment. Follow-up Visit 2 should occur 6 months after the last dose of trial treatment. After Follow-up Visit 2 subjects only need to be assessed every 9 weeks (63 ± 7 days) by radiologic imaging to monitor disease status, development of drug related SAEs and ECIs, and initiation of new antineoplastic therapy. Unless otherwise noted in the flow chart, every effort should be made to collect subject information until the start of new antineoplastic therapy, disease progression, or death, whichever occurs first.
3. Once a subject experiences disease progression or starts a new antineoplastic therapy, the subject moves into the Survival Follow-up Phase and should be contacted by telephone approximately every 2 months to assess for survival status and start of new antineoplastic therapy if applicable. Updated survival status may be requested by the Sponsor at any time during the course of the study. Upon Sponsor notification, all subjects who do not/will not have a scheduled study visit or study contact during the Sponsor-defined time period will be contacted for their survival status (excluding subjects who have a death event previously recorded).
4. Record all AEs occurring within 30 days after the last dose of trial treatment regardless of initiation of new therapy. Report all SAEs (related and unrelated to trial treatment), occurring within 90 days of the last dose of trial treatment or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever comes first. After this time, report only SAEs that are considered related to trial treatment.
5. Vital signs to include temperature, pulse, respiratory rate, blood pressure and weight.
6. The same imaging technique should be used in a subject as was used earlier in the trial. Imaging should continue until the start of a new antineoplastic therapy, documented disease progression, or death, whichever occurs first.
7. Subjects who discontinue trial treatment due to reasons other than disease progression should continue to be assessed every 9 weeks (63 ± 7 days) by radiologic imaging calculated from the date of randomization until initiation of a new cancer treatment or death.
8. Will be provided in full protocol for list of laboratory tests.
9. Analysis will be performed by a central laboratory only if the local laboratory is unable to perform this service.
10. Patient reported outcomes (PROs) are to be administered by trained site personnel and completed by subjects. It is strongly recommended that PROs are administered prior to adverse event evaluation and disease status notification starting with the EQ-5D, followed by EORTC QLQ-C30, and EORTC LC-13. All PROs are to be performed at the 30-day post-treatment discontinuation follow-up visit. If the subject does not complete the PROs, the MISS_MODE form must be completed to capture the reason the assessment was not performed.

6.3 Second Course Treatment and Follow-up Phase for Pembrolizumab Arm

	Second Course Treatment Cycles[1]													End of Second Course Treatment		Follow-up[16]			Survival Follow-up[11]
																1	**2**	**Every 3 Months after Visit 2**	**Approx. Every 2 Months**
Treatment Cycle/ Scheduled Time	1	2	3	4	5	6	7	8	9	10	11	12	13 and beyond	Discontinuation Visit	Safety Follow-up Visit[15]	Follow-up Visit 1	Follow-up Visit 2	Follow-up Visit 3 and Beyond	Survival Follow-up Visit 1 and Beyond
Scheduling Window (Days) [2]**:**	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	At study drug discontinuation ±3	30 days from last dose ±3	±7	±7	±7	±14
Administrative Procedures																			
Eligibility Criteria	X																		
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Subsequent Antineoplastic Therapy Status														X	X	X	X	X	X
Survival Status[11]	<--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	--------	-------->	X
Study Drug Administration																			
Pembrolizumab[13]	X	X	X	X	X	X	X	X	X	X	X	X	X						
Clinical Procedures/Assessments																			
Review Adverse Events[12]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Full Physical Examination	X																		
Directed Physical Examination		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Vital Signs[17]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
ECOG Performance Status	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		

	Second Course Treatment Cycles[1]													End of Second Course Treatment		Follow-up[16]			Survival Follow-up[11]
																1	2	Every 3 Months after Visit 2	Approx. Every 2 Months
Treatment Cycle/ Scheduled Time	1	2	3	4	5	6	7	8	9	10	11	12	13 and beyond	Discontinuation Visit	Safety Follow-up Visit[15]	Follow-up Visit 1	Follow-up Visit 2	Follow-up Visit 3 and Beyond	Survival Follow-up Visit 1 and Beyond
Scheduling Window (Days)[2]:	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	At study drug discontinuation ±3	30 days from last dose ±3	±7	±7	±7	±14
Laboratory Procedures/Assessments: Analysis Performed by Local Laboratory[5]																			
Pregnancy Test - Urine or Serum β-HCG[3]	X																		
PT/INR and aPTT[4]	X																		
CBC with Differential[6, 9]	X	X	X	X	X	X	X	X	X	X		X[9]		X	X[18]	X[18]	X[18]		
Comprehensive Chemistry Panel[6, 9]	X	X	X	X	X	X	X	X	X	X		X[9]		X	X[18]	X[18]	X[18]		
Urinalysis[10]	X				X				X				X[10]	X	X				
T3/FTE3, FT4 and TSH[6, 7]	X		X		X		X		X		X		X[7]	X	X[18]	X[18]	X[18]		
Efficacy Measurements																			
Tumor Imaging[8, 14]	X			X			X			X			X[8]	X	X[14]	X	X	X	

1. In general, assessments/procedures are to be performed on Day 1 and prior to the first dose of trial treatment for each cycle unless otherwise specified. Treatment cycles are 3 weeks (21 days). If treatment cycles are adjusted, all procedures except imaging will be completed according to the cycle number and not weeks on treatment; imaging will be performed every 9 weeks (63 ± 7 days) from the date of randomization regardless of any treatment delays.
2. In general, the window for each visit is ±3 days unless otherwise specified.
3. For women of childbearing potential (WOCBP), a urine pregnancy test will be performed within 72 hours prior to the first Second Course dose. 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.
4. Coagulation factors (PT/INR and aPTT) should be monitored closely throughout the trial for any subject receiving anticoagulant therapy.
5. Laboratory tests for determining eligibility for Second Course Phase are to be performed within 10 days prior to the first dose of pembrolizumab. See Section 7.1.3 for details regarding laboratory tests.
6. After the first dose, lab samples can be collected up to 3 days prior to the scheduled time point. Laboratory results must be known and acceptable prior to dosing. See Section 7.1.3 for details regarding laboratory tests.

	Second Course Treatment Cycles[1]													End of Second Course Treatment		Follow-up[16]			Survival Follow-up[11]
																1	2	Every 3 Months after Visit 2	Approx. Every 2 Months
Treatment Cycle/ Scheduled Time	1	2	3	4	5	6	7	8	9	10	11	12	13 and beyond	Discontinuation Visit	Safety Follow-up Visit[15]	Follow-up Visit 1	Follow-up Visit 2	Follow-up Visit 3 and Beyond	Survival Follow-up Visit 1 and Beyond
Scheduling Window (Days)[2]:	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	At study drug discontinuation ±3	30 days from last dose ±3	±7	±7	±7	±14

7. Thyroid function tests will be performed by a central laboratory only if the local laboratory is unable to perform this service. Thyroid function tests should be performed every other cycle.
8. Sponsor will collect radiological assessments for analysis by a central vendor. If the subject enters the Second Course Phase, Cycle 1 scan may be performed up to 30 days prior to the first dose of trial treatment in the Second Course Phase. Imaging will be performed every 9 weeks (63 ± 7 days) after the first dose of Second Course Phase trial treatment up until Cycle 13 and every 12 weeks (84 ± 7 days) thereafter. The timing of imaging should follow calendar days and should not be adjusted for delays in cycle starts or extension of pembrolizumab cycle frequencies. The same imaging technique should be used in a subject throughout the trial.
9. CBC with differentials and chemistry will be performed every cycle up to Cycle 10, then every other cycle thereafter.
10. Perform every 4 cycles.
11. Once a subject experiences disease progression or starts a new antineoplastic therapy, the subject moves into the Survival Follow-up Phase and should be contacted by telephone approximately every 2 months to assess for survival status and start of new antineoplastic therapy if applicable. Updated survival status may be requested by the Sponsor at any time during the course of the study. Upon Sponsor notification, all subjects who do not/will not have a scheduled study visit or study contact during the Sponsor defined time period will be contacted for their survival status (excluding subjects who have a death event previously recorded).
12. Record all AEs occurring within 30 days after the last dose of trial treatment. Report all SAEs (related and unrelated to trial treatment) occurring within 90 days following cessation of treatment or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier. After this time, report only SAEs that are considered related to trial treatment.
13. Pembrolizumab can be administered up to 17 trial treatment in Second Course Phase.
14. Subjects who discontinue trial treatment due to reasons other than disease progression should continue to be assessed every 9 weeks (63 ± 7 days) by radiologic imaging until the start of a new antineoplastic therapy, documented disease progression, or death, whichever occurs first. If trial treatment is discontinued after Cycle 13, tumor imaging should be performed every 12 weeks (84 days ± 7 days). Continued imaging is not needed for subjects who start another antineoplastic treatment. The same imaging technique should be used in a subject throughout the trial.
15. 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 antineoplastic treatment, whichever comes first. Subjects with an AE of Grade >1 will be further followed until the resolution of the AE to Grade 0-1 or until beginning of a new antineoplastic therapy, whichever occurs first. Subjects who are eligible for treatment with pembrolizumab during the Second Course Phase may have up to two Safety Follow-up Visits, one after the Treatment Phase and the second after the Second Course Phase.
16. Subjects who discontinue trial treatment for a reason other than disease progression will move into the Follow-up Phase and should be assessed every 9 weeks (63 ± 7 days) by radiologic imaging to monitor disease status. Follow-up Visit 1 should be scheduled 3 months after the last dose of trial treatment. Follow-up Visit 2 should occur 6 months after the last dose of trial treatment. After Follow-up Visit 2 subjects only need to be assessed every 9 weeks (63 ± 7 days) by radiologic imaging to monitor disease

	Second Course Treatment Cycles[1]													**End of Second Course Treatment**		**Follow-up[16]**			**Survival Follow-up[11]**
																1	**2**	**Every 3 Months after Visit 2**	**Approx. Every 2 Months**
Treatment Cycle/ Scheduled Time	1	2	3	4	5	6	7	8	9	10	11	12	13 and beyond	Discontinuation Visit	Safety Follow-up Visit[15]	Follow-up Visit 1	Follow-up Visit 2	Follow-up Visit 3 and Beyond	Survival Follow-up Visit 1 and Beyond
Scheduling Window (Days) [2]**:**	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	At study drug discontinuation ±3	30 days from last dose ±3	±7	±7	±7	±14

status, development of drug-related SAEs, and initiation of new antineoplastic therapy. Unless otherwise noted in the flow chart, every effort should be made to collect subject information until the start of new antineoplastic therapy, disease progression or death, whichever occurs first.

17. Vital signs to include temperature, pulse, respiratory rate, blood pressure, and weight.
18. Every effort should be made to collect blood samples at the Safety Follow-up Visit, Follow-up Visit 1, and Follow-up Visit 2 until the start of new antineoplastic therapy, disease progression or death, whichever comes first.

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 or qualified designee to ensure that the subject qualifies for the trial.

7.1.1.3 Subject Identification Card

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

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

7.1.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee. Medical history will include all active conditions, and any condition diagnosed within the prior 10 years that are considered to be clinically significant by the Investigator. In addition, record any prior cancer other than NCSLC even if diagnosed greater than 10 years prior to Visit 1. NSCLC history will be recorded separately and not listed as Medical History. Medical history will also include an assessment of smoking history.

7.1.1.5 Prior and Concomitant Medications Review

7.1.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the subject within 30 days before first dose of trial treatment. In addition, record all treatments for a prior cancer other than NSCLC even if taken greater than 30 days prior to first dose of trial treatment. Prior treatments for NSCLC will be recorded separately and not listed as a prior medication.

7.1.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the subject during the trial 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 Non-small cell lung cancer (NSCLC) Disease Details and Treatments

7.1.1.6.1 Disease Details

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

7.1.1.6.2 Prior Treatment

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

7.1.1.6.3 Subsequent Antineoplastic Therapy Status

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

7.1.1.7 Assignment of Screening Number

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

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

7.1.1.8 Assignment of Treatment/Randomization Number

All eligible subjects will be randomly allocated and will receive a treatment/randomization number. The treatment/randomization number identifies the subject for all procedures occurring after treatment allocation/randomization. Once a treatment/randomization number is assigned to a subject, it can never be re-assigned to another subject. IVRS/IWRS will be used in this study to randomize subjects and assign treatment/randomization number.

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

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

Interruptions from the protocol specified treatment plan for greater than 12 weeks between pembrolizumab (MK-3475) doses due to toxicity will 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 pembrolizumab (MK-3475) will be provided in the Procedures Manual.

Docetaxel will be prepared and administered as per the approved product label.

7.1.2 Clinical Procedures/Assessments

7.1.2.1 Adverse Event (AE) Monitoring

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

An immune related adverse event (irAE) may be defined as an adverse event of unknown etiology, associated with drug exposure and is consistent with an immune phenomenon. Efforts should be made to rule out neoplastic, infectious, metabolic, toxin or other etiologic causes prior to labeling an adverse event immune related. Immunological, serological and histological (biopsy) data should be used to support the diagnosis of an immune–related toxicity.

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

7.1.2.2 Physical Exam

7.1.2.2.1 Full Physical Exam

The investigator or qualified designee will perform a complete physical exam during the screening period and the end of treatment visit. Clinically significant abnormal findings should be recorded as medical history. After the first dose of trial treatment new clinically significant abnormal findings should be recorded as AEs.

7.1.2.2.2 Directed Physical Exam

For cycles that do not required a full physical exam per the Trial Flow Chart, the investigator or qualified designee will perform a directed physical exam as clinically indicated prior to trial treatment administration. New clinically significant abnormal findings should be recorded as AEs/SAEs.

7.1.2.3 Vital Signs

The investigator or qualified designee will take vital signs at screening, prior to the administration of trial treatment and during the Follow-up period as specified in the Trial Flow Chart. Vital signs include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at Visit 1 only.

7.1.2.4 12-Lead Electrocardiogram (ECG)

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

7.1.2.5 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status (see Section 12.4) at screening, prior to the administration of each dose of trial treatment and during the Follow-up period as specified in the Trial Flow Chart.

7.1.2.6 Tumor Imaging and Assessment of Disease

All imaging obtained on study will be submitted for blinded central radiologists' review. The process for image collection and transmission to the central vendor can be found in the Site Imaging Manual (SIM). Tumor imaging should be acquired by computed tomography (CT, strongly preferred). Magnetic resonance imaging (MRI) should be used when CT is contraindicated or for imaging the brain. The same imaging technique regarding modality and use of contrast should be used in a subject throughout the trial to optimize the visualization of existing and new tumor burden.

Imaging includes the chest, abdomen and pelvis.

Local site investigator/radiology assessment based on RECIST 1.1 will be used to determine subject eligibility. Although RECIST 1.1 references to maximum of 5 target lesions in total and 2 per organ, Merck allows maximum of 10 target lesions in total and 5 per organ. All scheduled images for all study subjects from the sites will be submitted to the central imaging vendor. In addition, additional imaging (including other modalities) that are obtained at unscheduled time points to determine disease progression, as well as imaging obtained for other reasons but captures radiologic progression, should be submitted to the central imaging vendor.

The central imaging vendor will verify PD following the first radiologic evidence of PD (based on local Investigator assessment). Expedited verification of radiologic PD by the central imaging vendor will be communicated to the trial site and Sponsor (See Section 7.1.2.6.3).

7.1.2.6.1 Initial Tumor Imaging

Initial tumor imaging must be performed within 28 days prior to the date of randomization. The site study team must review screening images to confirm the subject has measurable disease per RECIST 1.1.

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 28 days prior to the date of randomization and can be assessed by the central imaging vendor.

Subjects with previously treated brain metastases may participate provided they have stable brain metastases, i.e., without evidence of progression by imaging during screening; (confirmed by magnetic resonance imaging (MRI) if MRI was used at prior imaging, or confirmed by computed tomography (CT) imaging if CT used at prior imaging) for at least 4 weeks prior to the first dose of trial treatment. Any neurologic symptoms must have returned to baseline and subjects must have no clinical evidence of new or enlarging brain metastases, and have not used steroids for brain metastases for at least 3 days prior to trial initiation as per local site assessment. This exception does not include carcinomatous meningitis, as subjects with carcinomatous meningitis are excluded regardless of clinical stability.

7.1.2.6.2 Tumor Imaging During Trial

The first imaging assessment should be performed at 9 weeks (63 days ±7 days) from the date of randomization. Subsequent imaging should be performed every 9 weeks (63 days ±7 days) or more frequently if clinically indicated. Imaging timing should follow calendar days and should not be delayed for delays in cycle starts or extension of pembrolizumab (MK-3475) cycle intervals. Imaging should continue to be performed until disease progression verified by the central imaging vendor (unless site PI elects to continue treatment and follow irRECIST), the start of new anti-cancer treatment, withdrawal of consent, or death, whichever occurs first. All supplemental imaging must be submitted to the central imaging vendor.

Per RECIST 1.1, partial or complete response should be confirmed by a repeat radiographic assessment not less than 4 weeks from the date the response was first documented. The tumor imaging for confirmation of response may be performed at the earliest 4 weeks after the first indication of response, or at the next scheduled scan (i.e., 9 weeks later), whichever is clinically indicated. Subjects will then return to regular scheduled imaging, starting with the next scheduled imaging time point. Subjects who obtain a confirmation scan do not need to undergo the next scheduled tumor imaging if it is < 4 weeks later; tumor imaging may resume at the subsequent scheduled imaging time point.

Continue to perform imaging until whichever of the following occurs first:

- Initial site-assessed disease progression is verified by the central imaging vendor
- The start of new anti-cancer treatment
- Withdrawal of consent
- Death
- The end of the study

It is the discretion of the PI to continue to treat and image the subject at least 4 weeks after the first scan indicating progressive disease. irRECIST would then be followed by the site to determine if the follow-up scan confirms progressive disease (see Procedure Manual).

Subjects who have unconfirmed disease progression may continue on treatment and follow the regular imaging schedule intervals until progression is confirmed provided they have met the conditions detailed in Section 7.1.2.6.3.

Subjects who move into the Second Course Phase will continue to have scans performed every 9 weeks (63 ± 7 days) up to Cycle 13 and then every 12 weeks (84 ± 7 days).

7.1.2.6.3 Assessment of Disease

RECIST 1.1 will be applied by the central imaging vendor as the primary measure for assessment of tumor response, date of disease progression, and as a basis for all protocol guidelines related to disease status (e.g., discontinuation of study therapy). Initial tumor imaging showing site-assessed PD should be submitted to the central imaging vendor immediately. The site will be notified if the central imaging vendor verifies PD using

RECIST 1.1. Figure 2 illustrates the imaging flow involving verification of PD for clinically stable subjects.

7.1.2.6.3.1 irRECIST Assessment of Disease

irRECIST is RECIST 1.1 adapted as described below to account for the unique tumor response seen with immunotherapeutic drugs. irRECIST will be used by site investigator/local radiology review to assess tumor response and progression, and make treatment decisions. This data will be collected in the clinical database. Treatment efficacy based on irRECIST as assessed by central imaging vendor review will be evaluated retrospectively.

As noted above, per irRECIST, if tumor imaging shows initial PD, tumor assessment should be repeated ≥ 4 weeks later in order to confirm PD with the option of continuing treatment while awaiting radiologic confirmation of progression. Subjects who obtain a confirmation scan do not need to undergo scheduled tumor imaging if it is < 4 weeks later and may wait until the next scheduled imaging time point if clinically stable (see Section 4.2.3.2 and Table 5).

When feasible subjects should not be discontinued until progression is confirmed by the local site investigator/radiology assessment. This allowance to continue treatment despite initial radiologic progressive disease (PD) takes into account the observation that some subjects can have a transient tumor flare in the first few months after the start of immunotherapy, and then experience subsequent disease response. Subjects that are deemed clinically unstable are not required to have repeat tumor imaging for confirmation of PD. Tumor flare includes any of the following scenarios:

- Worsening of existing target lesion(s)
- Worsening of existing non-target lesion(s)
- Development of new lesions(s)

In subjects who have initial evidence of radiological PD by RECIST 1.1 as verified by central imaging vendor, it is at the discretion of the PI whether to continue a subject on study treatment until repeat imaging is obtained (using irRECIST for subject management; see Table 5). This clinical judgment decision by the site should be based on the subject's overall clinical condition, including performance status, clinical symptoms, and laboratory data. Subjects may receive study treatment and tumor assessment should be repeated ≥ 4 weeks later in order to confirm PD by irRECIST per site assessment. Clinical stability is defined as the following:

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

Any subject deemed **clinically unstable** should be discontinued from trial treatment at central verification of site- assessed first radiologic evidence of PD and is not required to have repeat imaging for PD confirmation.

In determining whether or not the tumor burden has increased or decreased per irRECIST, the local site investigator should consider all target and non-target lesions as well as any incremental new lesion(s).

Scenarios where PD is not confirmed at repeat imaging if ALL of the following occur by irRECIST:

- Target lesion sum of diameters is <20% or <5 mm absolute increase compared to Nadir
- Non-target disease resulting in initial PD is stable or qualitatively improved
- New lesion resulting in initial PD is stable or qualitatively improved
- No incremental new lesion(s) since last evaluation
- No incremental new non-target lesion progression since last evaluation

If repeat imaging does not confirm PD per irRECIST as assessed by the local site investigator and the subject continues to be clinically stable, study treatment and tumor imaging may continue per study schedule.

Scenarios where PD is confirmed at repeat imaging if ANY of the following occur by irRECIST:

- Target lesion sum of diameters remains ≥20 % and at least 5 mm absolute increase compared to nadir
- Non-target disease resulting in initial PD is qualitatively worse
- New lesion resulting in initial PD is qualitatively worse
- Additional new lesion(s) since last evaluation
- Additional new non-target lesion progression since last evaluation

If repeat imaging confirms PD due to any of the scenarios listed above, subject will be discontinued from study therapy.

NOTE: If a subject has confirmed radiographic progression (i.e. 2 scans at least 4 weeks apart demonstrating progressive disease) per irRECIST, but the subject is achieving a clinically meaningful benefit, and there is no further increase in the tumor burden at the confirmatory tumor imaging, an exception to continue treatment may be considered following consultation with the Sponsor. In this case, if treatment is continued, tumor imaging should continue to be performed following the intervals as outlined in sections 6.0 Study Flowchart and be submitted to the central imaging vendor.

Additional details about irRECIST are referenced in Merck TIP Sheet for RECIST 1.1 and irRECIST.

Table 5 Imaging and Treatment After 1st Radiologic Evidence of PD

	Clinically Stable		Clinically Unstable	
	Imaging	Treatment	Imaging	Treatment
First radiologic evidence of PD	Repeat imaging at > 4weeks at site to confirm PD	May continue study treatment at the Investigator's discretion while awaiting confirmatory scan by site by irRECIST	Repeat imaging at > 4 weeks to confirm PD per investigator discretion only	Discontinue treatment
Repeat scan confirms PD by irRECIST at the local site	No additional imaging Required*	Discontinue treatment (exception is possible upon consultation with Sponsor)	No additional imaging required	N/A
Repeat scan shows SD, PR or CR by irRECIST at the local site	Continue regularly scheduled imaging assessments	Continue study treatment at the Investigator's discretion	Continue regularly scheduled imaging assessments	May restart study treatment if condition has improved and/or clinically stable per Investigator's discretion. Next tumor image should occur according to the regular imaging schedule

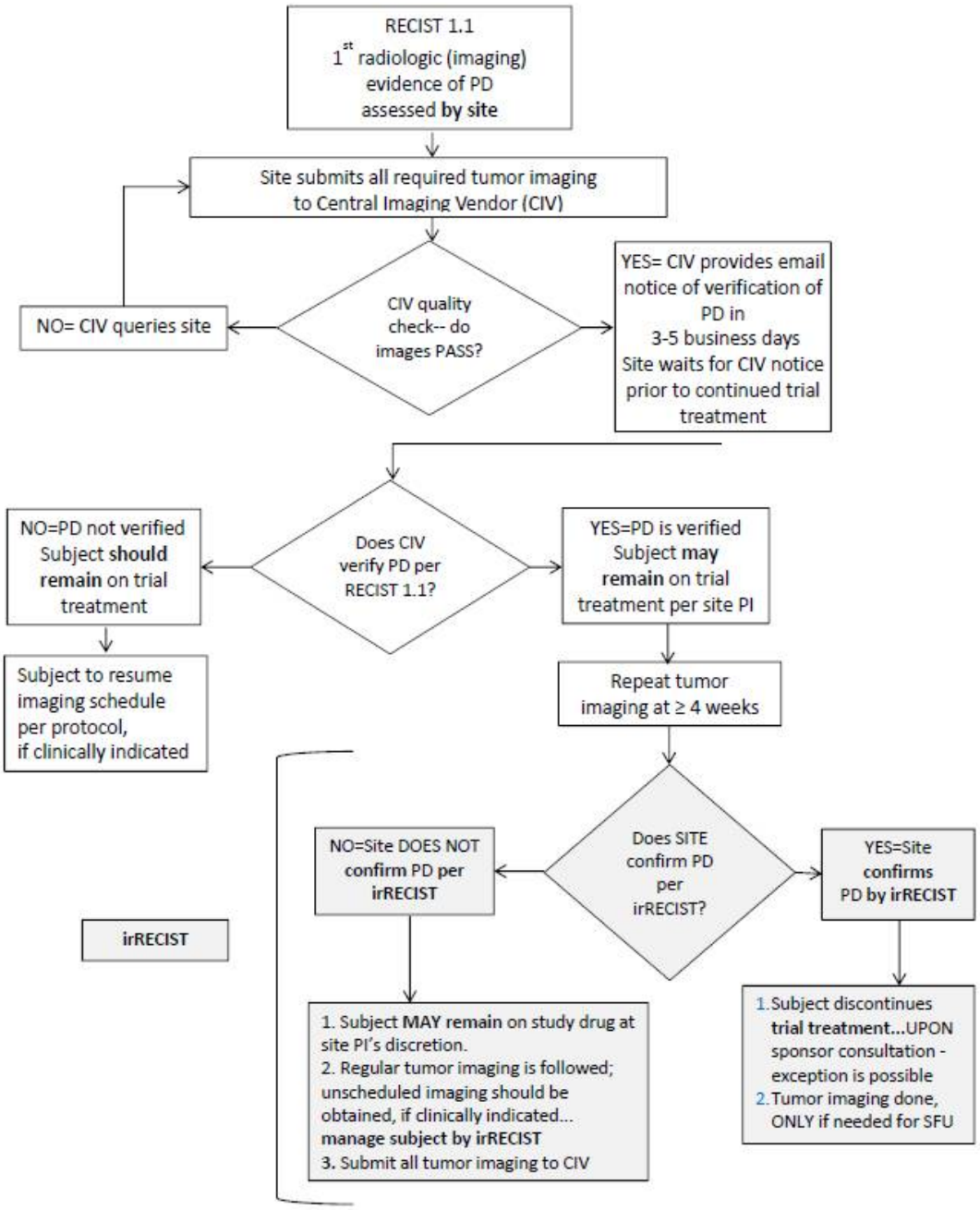

Figure 2 Imaging and Treatment for Clinically Stable Subjects after First Radiologic Evidence of PD Assessed by the Site

- In determining whether or not the tumor burden has increased or decreased, investigators should consider all target lesions as well as non-target lesions (please refer to the Imaging Tip Sheet). Subjects that are deemed clinically unstable are not required to have repeat imaging for confirmation. If radiologic progression is confirmed by subsequent scan then the subject will be discontinued from trial treatment. If radiologic progression is not confirmed, then the subject should resume or continue trial treatment and have their next scan according to the protocol schedule of every 9 weeks (63 ± 7 days).

  NOTE: If a subject has confirmed radiographic progression (i.e., 2 scans at least 4 weeks apart demonstrating progressive disease) per irRECIST, but the patient is achieving a clinically meaningful benefit, an exception to continue treatment may be considered following consultation with the Sponsor (see Procedure Manual).

irRECIST data will be collected in the clinical database.

In subjects who discontinue trial treatment, tumor imaging should be performed at the time of treatment discontinuation (± 4 week window). If a previous scan was obtained within 4 weeks prior to the date of discontinuation, then a scan at treatment discontinuation isn't mandatory. In subjects who discontinue trial treatment due to documented disease progression, this is the final required tumor imaging.

In subjects who discontinue trial treatment without documented disease progression, every effort should be made to continue monitoring their disease status by radiologic imaging every9 weeks (63 days ± 7 days) until (1) the start of new anti -cancer treatment, (2) disease progression, (3) death, or (4) the end of the study, whichever occurs first.

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 (from pre-trial to post-trial visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per subject can be found in the Procedures Manual.

7.1.3.1 Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

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

Table 6 Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit Hemoglobin Platelet count WBC (total and differential) Red Blood Cell Count Absolute Neutrophil Count Absolute Lymphocyte Count	Albumin Alkaline phosphatase Alanine aminotransferase (ALT) Aspartate aminotransferase (AST) Lactate dehydrogenase (LDH) Carbon Dioxide (CO_2 or bicarbonate) Creatinine or calculated creatinine clearance (CrCl) Uric acid Calcium Chloride Glucose Phosphorus Potassium Sodium Magnesium Total Bilirubin Direct and indirect Bilirubin Total protein Blood Urea Nitrogen** Urea Total Cholesterol Triglycerides	Blood Glucose Protein Specific gravity Microscopic exam, if abnormal results are noted Urine pregnancy test*	PT (INR) aPTT Triiodothyronine or Free Triiodothyronine (T3 or FT3) Free thyroxine (FT4) Thyroid stimulating hormone (TSH) Serum β-human chorionic gonadotropin (β-hCG)* Blood for FBR (if applicable) GFR HBsAg Anti HCV

* Perform on women of child bearing potential only. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required.
** Blood Urea Nitrogen is preferred, if not available urea may be test.

Laboratory tests for screening or entry into the Second Course Phase should be performed within 10 days prior to the first dose of trial treatment. After Cycle 1, pre-dose laboratory procedures can be conducted up to 72 hours prior to dosing.

Results must be reviewed by the investigator or qualified designee and found to be acceptable prior to each dose of trial treatment.

7.1.3.2 Molecular Testing

Site must be able to provide documentation of subject's tumor EGFR mutation and ALK translocation status. If the site is unable to provide this source documentation, then the Sponsor will offer this molecular testing of the tumor. Detailed instructions for tissue collection, processing and shipment are provided in the Procedures Manual.

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 Fresh Tumor Biopsy and/or Archival Tumor Tissue from the main study

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 Patient Reported Outcomes (PROs)

The EuroQol EQ-5D, EORTC QLQ C-30 and EORTC QLQ LC-13 questionnaires will be administered by trained site personal and completed by subjects. It is strongly recommended that the PROs are completed by the patient prior to drug administration, adverse event evaluation and disease status notification; an exception to this recommendation may occur at the treatment discontinuation visit. PROs will be administrated in the following order:

EuroQol EQ-5D first, then EORTC QLQ-C30, and lastly the EORTC LC-13 at the time points specified in the Trial Flow Chart.

7.1.4.4 Tumor Tissue Collection

Participation in this trial will be dependent upon supplying tumor tissue for PD-L1 testing from locations not radiated prior to biopsy; formalin-fixed specimens after the subject has been diagnosed with metastatic disease will be preferred for determination of PD -L1 status prior to randomization. Biopsies obtained prior to receipt of adjuvant/neoadjuvant therapy will be permitted if recent biopsy is not feasible. Only subjects whose tumors demonstrate evidence of PD-L1 expression (on the neoplastic cells) are eligible for enrollment. If the PD-L1 status is considered indeterminate for a submitted specimen, the subject will be excluded. Patients will be stratified between TPS ≥50% and TPS 1-49% before randomization. A fine needle aspirate or cytological specimen is not adequate for both archival and new tissue samples. Core needle or excisional biopsies, or resected tissue is required.

If the subject signs the Future Biomedical Research (FBR) consent, any leftover tissue biopsies that would ordinarily be discarded at the end of the main study will be retained for FBR, again providing the patient has signed the FBR consent.

Additional optional biopsies at approximately Week 6, Week 12 and Week 24 and at disease progression are highly desired when feasible, especially for those with an initial response to pembrolizumab (MK-3475). **THESE SAMPLES ARE TO BE COLLECTED ONLY FROM NON-TARGET LESIONS, TO AVOID ANY IMPACT ON irRECIST OUTCOMES.** Additional biopsy samples at disease progression can be obtained from the target lesion, but only after confirmation of disease progression by the Central Imaging Vendor.

Detailed instructions for tissue collection, processing and shipment are provided in the Procedures Manual. Older biopsy material or surgical specimens may be used to assess EGFR mutation status and ALK translocation status, if not already known when the patient signs informed consent.

7.1.4.5 Calibration of Critical Equipment

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

Critical Equipment for this trial includes:

Imaging equipment – as required for study objectives.

See protocol-specified guidance in the Administrative Binder, Procedures Manu al and Site Imaging Manual.

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

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

Approximately 42 days prior to randomization, potential subjects will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5.1. Screening procedures may be repeated after consultation with the Sponsor.

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. Screening procedures are to be completed within 42 days prior to the first dose of trial treatment except for the following:

- Laboratory tests are to be performed within 10 days prior to the first dose of trial treatment.
- For WOCBP, a urine pregnancy test will 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. Urine pregnancy isn't required at subsequent visits, but pregnancy tests (serum and/or urine tests) should be repeated if required by local guidelines. Monthly pregnancy testing should be conducted as per local regulations where applicable.
- Tumor imaging must be performed within 28 days 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 repeating a screening test if performed within the specified time frame and the results meet the inclusion/exclusion criteria.

7.1.5.2 Treatment Phase

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

7.1.5.3 Post-Treatment Follow-up Phase

Visit requirements are outlined in Section 6.0 - Trial Flow Chart. Specific procedure-related details are provided above in Section 7.1 - Trial Procedures. Patients will be followed for up to 2 years in Follow-up. If the subject experienced a CR, PR, or SD during the Treatment Phase on pembrolizumab, and then experiences PD at any time during the 2-year follow-up period, he/she will be eligible to receive up to 12 months of therapy with pembrolizumab in the Second Course Phase according to the criteria in Section 7.1.5.4.

7.1.5.3.1 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 antineoplastic treatment, whichever comes first. Subjects with an AE of Grade >1 will be further followed until the resolution of the AE to Grade 0-1 or until beginning of a new antineoplastic therapy, whichever occurs first. Subjects who are eligible per the requirements in Section 7.1.5.4 for treatment with pembrolizumab during the Second Course Phase may have up to two safety follow-up visits, one after the Treatment Phase and the second after the Second Course Phase.

7.1.5.3.2 Follow-up Visits

Subjects who discontinue trial treatment for a reason other than disease progression will move into the Follow-up Phase and should continue to be assessed every 9 weeks (63 ± 7 days) by radiologic imaging to monitor disease status. Follow-up Visit 1 should be scheduled 3 months after the last dose of trial treatment. Assessment for drug-related immune-related adverse events should occur at Follow-up Visit 1. Follow-up Visit 2 should occur 6 months after the last dose of trial treatment. After Follow-up Visit 2 subjects should continue to be assessed every 9 weeks (63 ± 7 days) by radiologic imaging to monitor disease status and initiation of new antineoplastic therapy. Unless otherwise noted in the flow chart, every effort should be made to collect subject information on the start of new antineoplastic therapy, until disease progression and or death.

7.1.5.3.3 Survival Follow-up

Once a subject stops receiving study medication, they will be followed for survival. Initially these data will be collected at the Safety Follow-up visit, the 3-month and 6-month Follow up visits, and any subsequent visits for imaging that may occur every 9 weeks until PD is identified. Once the subject stops the imaging assessments for this protocol every 9 weeks (e.g. for PD or starting a new antineoplastic therapy), the subject moves into the survival follow-up phase and should be contacted by telephone approximately every 2 months to assess for survival status. Post-study treatments and the subject's response to them will also be collected.

The Sponsor may request survival status data more frequently than every 9 weeks at specific time points during the study. For example, survival status may be requested prior to an external Data Monitoring Committee (eDMC) safety review, efficacy interim analyses and final analysis. All subjects who are in the Survival Follow-Up Phase and not known to have died prior to the request for these additional survival status time points will be contacted at that time.

7.1.5.4 Second Course Phase

Visit requirements are outlined in Section 6.0 - Trial Flow Chart.

Specific procedure-related details are provided above in Section 7.1 - Trial Procedures.

Subjects who were randomized to receive pembrolizumab may be eligible to receive pembrolizumab in the Second Course Phase of this study for up to 17 treatments (12 months) if the subject:

- Stopped their initial treatment with pembrolizumab/placebo after attaining a confirmed CR by central review, were treated for at least eight cycles with pembrolizumab/placebo, and received at least two treatments with pembrolizumab/placebo beyond the date when the initial CR was declared.

OR

- Had SD, PR or CR and stopped pembrolizumab treatment after 35 treatments for reasons other than disease progression or intolerability.

AND

- Experienced an investigator-determined confirmed radiographic disease progression according to irRECIST after stopping their initial treatment with pembrolizumab due to achievement of a confirmed CR.
- Did not receive any other systemic anti-cancer treatment since the last dose of pembrolizumab. (Local treatment such as radiation or surgery as anti-cancer therapy is allowed; Sponsor consultation must be obtained and subjects should have recovered completely from side effects of local procedures. In patients with brain metastases, neurological stability must be documented before initiating pembrolizumab.)
- Continues to meet inclusion criteria 8, 9, 13, 14 and 15.
- Does not meet exclusion criteria 2-16 and/or 17.

An objective response or progression of disease that occurs during the Second Course Phase for a subject will not be counted as an event for the primary analysis of either endpoint in this trial.

7.1.5.5 Survival Status

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

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 to be an adverse event.

All adverse events that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure. From the time of treatment allocation/randomization through 30 days following cessation of treatment, all adverse events must be reported by the investigator. Such events will be recorded at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in Section 7.2.3.1. The investigator will make every attempt to follow all subjects with non-serious adverse events for outcome.

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

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

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

For this trial, an overdose of pembrolizumab will be defined as any dose of 1000 mg or greater. No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, 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), including the pregnancy of a male subject's female partner that occurs during the trial.

Pregnancies and lactations of subjects and female partners of male subjects from the time 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 of subjects and female partners of male subjects that occur from the time of treatment allocation/randomization through 120 days following cessation of Sponsor’s product or 180 days after the last dose of docetaxel, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, must be reported. All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

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

7.2.3 Immediate Reporting of Adverse Events to the Sponsor

7.2.3.1 Serious Adverse Events

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

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

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

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

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

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

For the time period beginning at treatment allocation/randomization through 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study (see 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 outside of the time period specified in the previous paragraph also must be reported immediately to the Sponsor.

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

7.2.3.2 Events of Clinical Interest

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

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

For the time period beginning at treatment allocation/randomization through 30 days following cessation of treatment, any ECI, or follow up to an ECI, whether or not related to

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

Events of clinical interest for this trial include:

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

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

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

7.2.3.3 Protocol-Specific Exceptions to Serious Adverse Event Reporting

Efficacy endpoints as outlined in this section will not be reported to the Sponsor as described in Section 7.2.3. - 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, i.e., per ICH Topic E6 (R1) Guidelines for Good Clinical Practice.

7.3 TRIAL GOVERNANCE AND OVERSIGHT

7.3.1 Executive Oversight Committee

The Executive Oversight Committee (EOC) comprises members of Sponsor Senior Management. The EOC will receive and decide upon any recommendations made by the external Data Monitoring Committee (eDMC) regarding the trial.

7.3.2 Data Monitoring Committee

To supplement the routine trial monitoring outlined in this protocol, an external Data Monitoring Committee (eDMC) will monitor the interim data from this trial. The voting members of the committee are external to the Sponsor. The members of the eDMC must not be involved with the trial in any other way (e.g., they cannot be trial investigators) and must have no competing interests that could affect their roles with respect to the trial.

The eDMC will make recommendations to the EOC regarding steps to ensure both subject safety and the continued ethical integrity of the trial. Also, the eDMC will review interim trial results, consider the overall risk and benefit to trial participants and recommend to the EOC if the trial should continue in accordance with the protocol.

Specific details regarding responsibilities and governance, including the roles and responsibilities of the various members and the Sponsor protocol team; meeting facilitation; the trial governance structure; and requirements for and proper documentation of eDMC reports, minutes, and recommendations will be described in a separate charter that is reviewed and approved by the eDMC. The eDMC will monitor the trial at an appropriate frequency, as described in the detailed eDMC charter. The eDMC will also make recommendations to the Sponsor protocol team regarding steps to ensure both subject safety and the continued ethical integrity of the trial.

8.0 STATISTICAL ANALYSIS PLAN

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

8.1 Statistical Analysis Plan Summary

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

Study Design Overview	A Multinational, Multicenter, Phase III, Randomized Open-label Trial of Pembrolizumab versus Docetaxel in Previously Treated Subjects with Non-Small Cell Lung Cancer
Treatment Assignment	Subjects will be randomized in a 1:1 ratio to receive pembrolizumab (MK-3475) or docetaxel. This is an open-label study.
Analysis Populations	Efficacy: Intention to Treat (ITT) Safety: All Subjects as Treated (ASaT)
Primary Endpoint(s)	1. Overall survival (OS) in the TPS ≥50% stratum 2. Overall survival (OS) in the TPS ≥1% population 3. Progression free survival (PFS) per RECIST 1.1 assessed by blinded central radiologists' review in the TPS ≥50% stratum 4. PFS per RECIST 1.1 assessed by blinded central radiologists' review s in the TPS ≥1% population.
Statistical Methods for Key Efficacy Analyses	The primary hypotheses will be evaluated by comparing pembrolizumab (MK-3475) to the control on OS and PFS using a Log-rank test. Estimation of the hazard ratio will be done using a Cox proportional hazard model. Event rates over time will be estimated within each treatment group using the Kaplan-Meier method.
Statistical Methods for Key Safety Analyses	The analysis of safety results will follow a tiered approach. Tier 2 parameters will be assessed via point estimates with 95% confidence intervals provided for between-group comparisons; only point estimates by treatment group are provided for Tier 3 safety parameters. There are no Tier 1 events in this trial. The between- treatment difference will be analyzed using the Miettinen and Nurminen method.
Interim Analyses	One interim analysis will be performed in this study. Details are provided in Section 8.7. 1) Timing: About 30 months after study starts. 2) Purpose: • Demonstrate superiority of pembrolizumab (MK-3475) in OS in TPS ≥50% stratum first, if achieved, and then sequentially demonstrate superiority of pembrolizumab (MK-3475) in OS in TPS ≥1% population. • If the OS superiority is demonstrated in the TPS ≥50% stratum and TPS ≥1% population in the interim analysis (IA) or final analysis, then demonstrate superiority of pembrolizumab (MK-3475) in PFS in TPS ≥50% stratum and TPS ≥1% population sequentially.
Multiplicity	The overall type I error is strongly controlled at 2.5% (one-sided). See Section 8.8 Multiplicity for the Type I error control strategy.

Sample Size and Power	The study will randomize approximately 216 subjects with TPS ≥50% in a 1:1 ratio into pembrolizumab (MK-3475) arm and docetaxel arm. The overall sample size for this study is projected to be approximately 400. The number of subjects randomized in the TPS ≥50% stratum drives the end of enrollment. The study is calendar time and final analysis is planned approximately 36 months after the first subject randomized, at which time approximately 150 deaths will have been observed among two arms from the TPS ≥50% stratum. For primary endpoint OS in the TPS ≥50% stratum, the trial has ~87% power to demonstrate that pembrolizumab (MK-3475) is superior to docetaxel at a one-sided 2.5% alpha-level, if the underlying hazard ratio of OS is 0.6. The power will increase to approximately 90% if the underlying hazard ratio of OS is 0.58[34]. For OS in the TPS ≥1% population, the trial has ~90% power to demonstrate that pembrolizumab (MK-3475) is superior to docetaxel at a one-sided 2.5% alpha-level, if the underlying hazard ratio of OS is 0.68 at approximate 280 events..

8.2 Responsibility for Analyses/In-House Blinding

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

The IVRS vendor/Sponsor will generate the randomized allocation schedule(s) for study treatment assignment for this protocol, and the randomization will be implemented in IVRS.

Although the trial is open-label, analyses or summaries generated by randomized treatment assignment and actual treatment received will be limited and documented. In addition, the blinded central radiologist will perform the central imaging review without knowledge of treatment group assignment. The sites will be notified of the positive and negative PD_L1 results for enrollment but the details of PD_L1 score will not be shared with the sites and will be directly transferred to IVRS for stratification. The sites, the principal investigators, sub-investigators and their staff as well as Merck's clinical research coordinators (CRAs) involved in on-site monitoring will remain blinded to details PD_L1 score.

The planned interim analysis is described in Section 8.7. The eDMC will serve as the primary reviewer of the unblinded results of the interim analyses and will make recommendations for discontinuation of the study or modification to an executive oversight committee of the SPONSOR. Depending on the recommendation of the eDMC, the Sponsor may prepare a regulatory submission. If the eDMC recommends modifications to the design of the protocol or discontinuation of the study, this executive oversight committee may be unblinded to results at the treatment level in order to act on these recommendations. Additional logistical details will be provided in the eDMC Charter.

8.3 Hypotheses/Estimation

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

8.4 Analysis Endpoints

8.4.1 Efficacy Endpoints

Primary

Overall Survival (OS)

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

Progression-free survival (PFS) – RECIST 1.1 by blinded central radiologists' review

Progression-free-survival (PFS) is defined as the time from randomization to the first documented disease progression per RECIST 1.1 based on blinded central radiologists' review or death due to any cause, whichever occurs first. See Section 8.6.1 for the censoring rules.

Secondary

Objective Response Rate (ORR) –RECIST 1.1 by blinded central radiologists' review

Objective response rate is defined as the proportion of the subjects in the analysis population who have a complete response (CR) or partial response (PR).

Duration of Response (DOR) –RECIST 1.1 by blinded central radiologists' review

For subjects who demonstrated CR or PR, duration of response is defined as the time from first documented evidence of CR or PR until disease progression per RECIST 1.1 or death due to any cause, whichever occurs first. See Section 8.6.1 for the censoring rules.

8.4.2 Safety Endpoints

Safety measurements are described in Section 4.2.3.2 Safety Endpoints and Section 7.

Safety and tolerability will be assessed by clinical review of all relevant parameters including adverse events (AEs), laboratory tests, and vital signs. Furthermore, specific events will be collected and designated as events of clinical interest (ECIs) as described in Section 7.2.3.

There are no "Tier 1" events in this trial. In addition, the broad clinical and laboratory AE categories consisting of the percentage of subjects with any AE, any drug related AE, any Grade 3-5 AE, any serious AE, any AE which is both drug-related and Grade 3-5, any AE which is both serious and drug-related, dose modification due to AE, and who discontinued due to an AE, and death will be considered Tier 2 endpoints. AEs (specific terms as well as system organ class terms) will be classified as belonging to "Tier 2" or "Tier 3", based on the number of events observed. Membership in Tier 2 requires that at least 4 subjects in any treatment group exhibit the event; all other AEs and predefined limits of change will belong to Tier 3.

8.5 Analysis Populations

8.5.1 Efficacy Analysis Populations

The Intention-to-Treat (ITT) population will serve as the population for primary efficacy analysis. All randomized subjects will be included in this population. Subjects will be included in the treatment group to which they are randomized.

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

8.5.2 Safety Analysis Populations

The All Subjects as Treated (ASaT) population will be used for the analysis of safety data in this study. The ASaT population consists of all randomized subjects who received at least one dose of study treatment. Subjects will be included in the treatment group corresponding to the study treatment they actually received for the analysis of safety data using the ASaT population. For most subjects this will be the treatment group to which they are randomized. Subjects who take incorrect study treatment for the entire treatment period will be included in the treatment group corresponding to the study treatment actually received. Any subject who receives the incorrect study medication for one cycle but receives the correct treatment for all other cycles will be analyzed according to the correct treatment group and a narrative will be provided for any events that occur during the cycle for which the subject is incorrectly dosed.

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

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

8.6 Statistical Methods

This section describes the statistical methods that address the primary and secondary objectives. Methods related to exploratory objectives will be described in the supplemental SAP.

8.6.1 Statistical Methods for Efficacy Analyses

Efficacy results that will be deemed to be statistically significant after consideration of the Type I error control strategy are described in Section 8.8, Multiplicity. Nominal p-values will be computed for other efficacy analyses, but should be interpreted with caution due to potential issues of multiplicity.

8.6.1.1 Overall Survival (OS)

The non-parametric Kaplan-Meier method will be used to estimate the survival curve**s** in each treatment group. The treatment difference in survival will be assessed by the log-rank test. A Cox proportional hazard model with Efron's method of tie handling will be used to assess the magnitude of the treatment difference (i.e., the hazard ratio). The hazard ratio and its 95% confidence interval from the Cox model with a single treatment covariate will be

reported. The stratification factor used for randomization (PD-L1 expression (TPS ≥50% vs. 1-49% positive)) will be applied to both the stratified log-rank test and the stratified Cox model for analysis of TPS ≥1% subjects. Unstratified log-rank test and the unstratified Cox model will be used for the analysis of TPS ≥50% stratum.

Subjects in the Docetaxel arm may switch to another anti PD-1 treatment following the verification of progressive disease by blinded central radiologists' review. As an exploratory analysis, the Rank Preserving Structural Failure Time (RPSFT) model proposed by Robins and Tsiatis (1989) [32] may be used to adjust for the effect of crossover to other PD-1 therapies on OS.

Further details of sensitivity analyses will be described in supplemental SAP.

8.6.1.2 Progression-Free Survival (PFS)

The non-parametric Kaplan-Meier method will be used to estimate the PFS curve in each treatment group. The treatment difference in PFS will be assessed by the log-rank test. A Cox proportional hazard model with Efron's method of tie handling will be used to assess the magnitude of the treatment difference (i.e., hazard ratio) between the treatment arms. The hazard ratio and its 95% confidence interval from the Cox model with Efron's method of tie handling and with a single treatment covariate will be reported. The stratification factor used for randomization (PD-L1 expression (TPS ≥50% vs. 1-49% positive)) will be applied to both the stratified log-rank test and the stratified Cox model for analysis of TPS ≥1% subjects. Unstratified log-rank test and the unstratified Cox model will be used for the analysis of TPS ≥50% stratum.

Since disease progression is assessed periodically, progressive disease (PD) can occur anytime in the time interval between the last assessment where PD was not documented and the assessment when PD is documented. For the primary analysis, for the subjects who have PD, the true date of disease progression will be approximated by the date of the first assessment at which PD is objectively documented per RECIST 1.1 by blinded central radiologists' review. Death is always considered as a confirmed PD event. Subjects without documented PD/death will be censored at the last disease assessment date.

In order to evaluate the robustness of the PFS endpoint per RECIST 1.1 by blinded central radiologists' review, we will perform one primary and two sensitivity analyses with a different set of censoring rules. For the primary analysis, if the events (PD or death) are immediately after more than one missed disease assessment, the data are censored at the last disease assessment prior to missing visits. Also data after new anti-cancer therapy are censored at the last disease assessment prior to the initiation of new anti-cancer therapy. The first sensitivity analysis follows the intention-to-treat principle. That is, PDs/deaths are counted as events regardless of missed study visits or initiation of new anti-cancer therapy. The second sensitivity analysis considers initiation of new anticancer treatment or discontinuation of treatment due to reasons other than complete response (whichever is later) to be a PD event for subjects without documented PD or death. The censoring rules for primary and sensitivity analyses are summarized in Table 8. In case there is an imbalance between the treatment groups on disease assessment schedules or censoring patterns, a likelihood based score test for interval censored data, which modifies the Cox proportional hazard model for interval censored data [28], may be used as a supportive analysis for the

PFS endpoint. The interval will be constructed so that the left endpoint is the date of the last disease assessment without documented PD and the right endpoint is the date of documented PD or death, whichever occurs earlier.

Table 8 Censoring rules for Primary and Sensitivity Analyses of PFS

Situation	Primary Analysis	Sensitivity Analysis 1	Sensitivity Analysis 2
PD or death documented after ≤ 1 missed disease assessment, and before new anti-cancer therapy, if any	Progressed at date of documented PD or death	Progressed at date of documented PD or death	Progressed at date of documented PD or death
PD or death documented immediately after ≥ 2 consecutive missed disease assessments or after new anti-cancer therapy, if any	Censored at last disease assessment prior to the earlier date of ≥ 2 consecutive missed disease assessment and new anti-cancer therapy, if any	Progressed at date of documented PD or death	Progressed at date of documented PD or death
No PD and no death; and new anticancer treatment is not initiated	Censored at last disease assessment	Censored at last disease assessment	Progressed at treatment discontinuation due to reasons other than complete response; otherwise censored at last disease assessment if still on study treatment or completed study treatment.
No PD and no death; new anticancer treatment is initiated	Censored at last disease assessment before new anticancer treatment	Censored at last disease assessment	Progressed at date of new anticancer treatment

The proportional hazards assumption on PFS will be examined using both graphical and analytical methods if warranted. The log[-log] of the survival function vs. time for PFS will be plotted for the comparison between pembrolizumab (MK-3475) and the docetaxel arm. If the curves are not parallel, indicating that hazards are not proportional, supportive analyses may be conducted to account for the possible non-proportional hazards effect associated with

immunotherapies: for example, using Restricted Mean Survival Time (RMST) method [29], parametric method [30], etc.

Further details of sensitivity analyses will be described in supplemental SAP.

8.6.1.3 Objective Response Rate (ORR)

Miettinen and Nurminen's method will be used for the comparison of the ORR between two treatment groups in the analysis for TPS ≥50% stratum and TPS ≥1% subjects respectively. The difference in ORR and its 95% confidence interval from the Miettinen and Nurminen's method will be reported respectively. Stratified Miettinen and Nurminen's method with the stratification factor PD-L1 expression (TPS ≥ 50% vs. 1-49% positive) (See Section 5.4) will be applied to the analysis for TPS ≥1% subjects with strata weighting by sample size. Unstratified Miettinen and Nurminen's method will be applied to the analysis for TPS ≥50% subjects.

8.6.1.4 Duration of Response (DOR)

For subjects who demonstrate CR or PR, duration of response is defined as the time from first documented evidence of CR or PR until disease progression or death due to any cause, whichever occurs first.

Subjects who are alive, have not progressed, have not initiated new anti-cancer treatment, and have not been determined to be lost to follow-up are considered ongoing responders at the time of analysis. Censoring rules for DOR are summarized in Table 9.

Table 9 Censoring Rules for DOR

Situation	Date of Progression or Censoring	Outcome
No progression nor death, no new anti-cancer therapy initiated	Last adequate disease assessment	Censor (non-event)
No progression nor death, new anti-cancer therapy initiated	Last adequate disease assessment before new anti-cancer therapy initiated	Censor (non-event)
Death or progression immediately after ⩾ 2 consecutive missed disease assessments or after new anti-cancer therapy, if any	Earlier date of last adequate disease assessment prior to ⩾ 2 missed adequate disease assessments and new anti-cancer therapy, if any	Censor (non-event)
Death or progression after ⩽ 1 missed disease assessments and before new anti-cancer therapy, if any	PD or death	End of response (Event)
A missed disease assessment includes any assessment that is not obtained or is considered inadequate for evaluation of response.		

Table 10 summarizes the primary analysis approach for primary and secondary efficacy endpoints. Sensitivity analysis methods are described above for each endpoint.

The strategy to address multiplicity issues with regard to multiple efficacy endpoints, multiple populations, and interim analyses is described in Section 8.7 Interim Analyses and Final Analyses and in Section 8.8 Multiplicity.

Table 10 Analysis Strategy for Key Efficacy Endpoints

Endpoint/Variable (Description, Time Point)	Statistical Method†	Analysis Population	Missing Data Approach
Primary Hypothesis #1			
OS in TPS ≥50% stratum	Test: Unstratified Log-rank test Estimation: Unstratified Cox model with Efron's tie handling method	ITT in TPS ≥ 50% stratum	Censored at last known alive date
Primary Hypothesis #2			
OS in TPS ≥1% population	Test: Stratified Log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT	Censored at last known alive date
Primary Hypothesis #3			
PFS per RECIST 1.1 blinded central radiologists' review in TPS ≥50% stratum	Test: Unstratified Log-rank test Estimation: Unstratified Cox model with Efron's tie handling method	ITT in TPS ≥50% stratum	• Primary censoring rule • Sensitivity analysis 1 • Sensitivity analysis 2 (More details are in Table 8)
Primary Hypothesis#4			
PFS per RECIST 1.1 by blinded central radiologists' review in TPS ≥1% population	Test: Stratified Log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT	• Primary censoring rule • Sensitivity analysis 1 • Sensitivity analysis 2 (More details are in Table 8)

Endpoint/Variable (Description, Time Point)		Statistical Method†	Analysis Population	Missing Data Approach
Secondary Endpoints				
ORR	per RECIST 1.1 by blinded central radiologists' review	M & N method‡	ITT	Subjects with missing data are considered non-responders
Duration of Response	per RECIST 1.1 by blinded central radiologists' review	Summary statistics using Kaplan-Meier method	All responders in ITT	Censored at last assessment date if responding at the time of analysis

† Statistical models are described in further detail in the text. For stratified analyses, the stratification factor used for randomization (PD-L1 expression (TPS ≥ 50% vs. 1-49% Positive)) will be applied to the analysis.

‡ Miettinen and Nurminen method.

8.6.2 Statistical Methods for Safety Analyses

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

The analysis of safety results will follow a tiered approach (Table 11). The tiers differ with respect to the analyses that will be performed. AEs (specific terms as well as system organ class terms) and events that meet predefined limits of change in laboratory, vital signs, and ECG parameters are either prespecified as "Tier 1" endpoints or will be classified as belonging to "Tier 2" or "Tier 3" based on observed proportions of participants with an event.

Tier 1 Events

Safety parameters or AEs of special interest that are identified a priori constitute "Tier 1" safety endpoints that will be subject to inferential testing for statistical significance. AEs that are immune-mediated or potentially immune-mediated are well documented and will be evaluated separately; however, these events have been characterized consistently throughout the pembrolizumab clinical development program, and determination of statistical significance is not expected to add value to the safety evaluation. Finally, there are no known AEs associated with participants with NSCLC for which determination of a p value is expected to impact the safety assessment. Therefore, there are no Tier 1 events for this protocol.

Tier 2 Events

Tier 2 parameters will be assessed via point estimates with 95% CIs provided for differences in the proportion of participants with events using the Miettinen and Nurminen method, an unconditional, asymptotic method.

Membership in Tier 2 requires that at least 10% of participants in any treatment group exhibit the event; all other AEs and predefined limits of change will belong to Tier 3. The threshold of at least 10% of participants was chosen for Tier 2 events because the population enrolled in this study are in critical conditions and usually experience various AEs of similar types regardless of treatment; events reported less frequently than 10% of participants would obscure the assessment of the overall safety profile and add little to the interpretation of potentially meaningful treatment differences. In addition, Grade 3 to 5 AEs (≥5% of participants in one of the treatment groups) and SAEs (≥5% of participants in one of the treatment groups) will be considered Tier 2 endpoints. Because many 95% CIs may be provided without adjustment for multiplicity, the CIs should be regarded as a helpful descriptive measure to be used in safety review, not a formal method for assessing the statistical significance of the between-group differences.

Tier 3 Events

Safety endpoints that are not Tier 1 or 2 events are considered Tier 3 events. Only point estimates by treatment group are provided for Tier 3 safety parameters.

Continuous Safety Measures

For continuous measures such as changes from baseline in laboratory, vital signs, and ECG parameters, summary statistics for baseline, on-treatment, and change from baseline values will be provided by treatment group in table format.

Table 11 Analysis Strategy for Safety Parameters

Safety Tier	Safety Endpoint	95% CI for Treatment Comparison	Descriptive Statistics
Tier 2	Any AE (≥ 10% of participants in one of the treatment groups)	X	X
	Any Grade 3 to 5 AE (≥ 5% of participants in one of the treatment groups)	X	X
	Any serious AE (≥ 5% of participants in one of the treatment groups)	X	X
Tier 3	Any AE		X
	Change from baseline results (laboratory test toxicity grade)		X
AE = adverse event; CI = confidence interval; X = results will be provided.			

8.6.3 Summaries of Demographic and Baseline Characteristics

The comparability of the treatment groups for each relevant characteristic 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 randomized, and the primary reason for discontinuation will be displayed. Demographic variables (such as age) and baseline characteristics will be summarized by treatment either by descriptive statistics or categorical tables.

8.7 Interim Analyses

There is one planned interim analysis in this trial.

The interim analysis will be performed about 30 months after first subject randomized. By then, about 125 deaths are projected to occur in the subjects with TPS⩾50%. The actual HR boundary for interim analysis will be determined from the number of OS events observed at the time of the interim analysis using the alpha spending function.

The primary objective of this interim analysis is to demonstrate that pembrolizumab (MK-3475) arm is superior to the docetaxel arm in OS in TPS ≥50% stratum at the 1.41% significance level, regardless of the actual number of deaths observed at the IA. A p-value of 1.41% (one-sided) for OS approximately corresponds to an empirical hazard ratio of 0.6737. A positive finding on OS may lead to regulatory filing for drug approval upon discussion with regulatory agencies. PFS analysis using the interim data will be the final analysis for the PFS hypotheses.

Table 12 summarizes the timing, sample size and decision guidance of the interim analysis and final analysis in the hypothetical scenario where the numbers of deaths at IA and FA are assumed to be the same as the projected (i.e., 125 for IA and 150 for FA in the subjects with TPS>50%). The IA p-value boundary will be fixed. The IA HR boundary will be re-calculated if the actual number of IA death events is altered from the expected. The FA p-value and HR boundaries will be re-calculated if the actual number of IA or FA death events is altered from the expected; the actual FA boundaries will be based on the observed number of death events at IA and FA.

Superiority of OS in both TPS ≥50% stratum and ≥1% population needs to be demonstrated in order for the eDMC to recommend stopping the trial due to efficacy. All details will be described in the eDMC Charter.

Table 12 Summary of Timing, Sample Size and Decision Guidance of Interim Analyses and Final Analyses

Analysis	Criteria for Conduct of Analysis	Value	Efficacy
Interim Analysis	~ 30 months after trial starts[2] (~125 OS events have been observed in TPS≥50% stratum)	p-value (1-sided) at boundary ~ HR at boundary	<=0.0141 0.6737
Final Analyses	~ 36 months after trial starts[2] (~150 OS events have been observed in TPS≥50% stratum)	p-value (1-sided) at boundary ~ HR at boundary	<=0.0210 0.7160

[1] In this hypothetical scenario, the numbers of deaths at IA and FA are assumed to be the same as the projected. The IA HR boundary will be re-calculated if the actual number of IA death events is altered from the expected. The FA p-value and HR boundaries will be re-calculated if the actual number of IA or FA death events are altered from the expected; the actual FA boundaries will be based on the observed number of death events at IA and FA

[2] Trial start is defined as the date when the first subject was randomized.

8.8 Multiplicity

The multiplicity strategy specified in this section will be applied to the TPS ≥50% stratum and the TPS ≥1% population for the testing of the OS hypotheses and the PFS hypotheses. The overall type I error is strongly controlled at 2.5% (one-sided). The following hypotheses will be tested sequentially at the type I error rate of 2.5% (one-sided) in the following order:

- Superiority of pembrolizumab (MK-3475) in OS in the TPS ≥50% stratum;
- Superiority of pembrolizumab (MK-3475) in OS in the overall TPS ≥1% population;
- Superiority of pembrolizumab (MK-3475) in PFS in the TPS ≥50% stratum;
- Superiority of pembrolizumab (MK-3475) in PFS in the overall TPS ≥1% population.

Testing will stop with the first of these tests failing to reach statistical significance and all subsequent tests would not be considered for statistical significance. The sequential hypothesis testing for OS can continue across the interim and final analyses.

The type I error rates for the interim analysis and final analysis which will allow tight control of the overall type I error for testing the OS hypothesis in the TPS ≥50% stratum will be derived using the alpha-spending function approach. The OS efficacy boundary will be set using the O'Brien-Fleming approach with the total alpha 2.5% (one-sided) and specified calendar time fraction (0.83 for interim analysis and 1.00 for final analysis, respectively). No futility boundary will be set.

Both IA and FA will be conducted based on calendar time. Specifically, IA and FA will occur about 30 months and about 36 months after the date when the first subject was randomized. The cumulative alpha (one-sided) spending at the planned time of IA and FA becomes 1.41% and 2.5%, regardless of the actual number of deaths observed at the IA and

FA. The actual HR boundary at IA will be calculated based on the cumulative alpha spent and actual number of deaths observed at IA; the actual p value boundary and HR boundary at FA will then be calculated based on the cumulative alpha spent and actual number of deaths observed at IA and FA.

If the pembrolizumab (MK-3475) arm demonstrates superior OS in the TPS ≥50% stratum at the interim analysis, the OS hypothesis in the TPS ≥1% population will be tested based on a group sequential approach with the cumulative alpha spent up to the IA as the same as the alpha spent for testing the OS hypothesis in the TPS ≥50% stratum up to that IA.

The primary testing of the PFS hypothesis will only be conducted on the interim analysis data, and only if OS superiority is demonstrated in both of the TPS≥50% stratum and the TPS ≥ 1% population. Since the time of the interim analysis is the only analysis for PFS, the p-values for PFS primary hypothesis tests will be sequentially compared to 2.5% (one-sided).

8.9 Sample Size and Power Calculations

The study will randomize approximately 216 subjects with TPS ≥50% in a 1:1 ratio into pembrolizumab (MK-3475) arm and docetaxel arm. The overall sample size for this study is projected to be approximately 400. The number of subjects randomized in the TPS ≥50% stratum drives the end of enrollment.

The study is calendar time driven and will complete after approximately 36 months after the first subject randomized, at which time approximately 150 deaths will have been observed between the two arms in the TPS ≥50% stratum. With 150 deaths, the study has approximately 87% power to detect a 0.6 hazard ratio on OS at alpha=2.50% (one-sided) in the TPS ≥50% stratum. The power will increase to approximately 90% if the underlying hazard ratio of OS is 0.58 [34]. By the time when 150 deaths are observed in the TPS ≥50% stratum, the expected number of deaths is about 280 in the TPS ≥1% population. With 280 deaths, the study has approximately 90% power to detect a 0.68 hazard ratio on OS at alpha=2.5% (one-sided) in the overall TPS ≥1% population. Details on the nominal alpha and the approximate efficacy boundary at each interim analysis are summarized in Section 8.7.

The power calculation is based on the following assumptions for subjects in the TPS ≥50% stratum and TPS ≥1% population: 1) OS follows an exponential distribution with a median of 10 months in the docetaxel arm; 2) An enrollment period of 24 months; 3) A yearly drop-out rate of 2%.

8.10 Subgroup Analyses and Effect of Baseline Factors

To determine whether the treatment effect is consistent across various subgroups, the estimate of the between-group treatment effect (with a nominal 95% CI) for the primary endpoints will be estimated and plotted within each category of the following classification variables. These subgroup analyses would be carried out in TPS ≥ 50% stratum and TPS ≥ 1% population as applicable:

- Age category (≤65 vs. >65 years)
- Sex (Female vs. Male)
- ECOG Performance Scale (0 vs. 1)

- Disease Status (Locally advanced vs. Metastatic)
- PD-L1 expression (TPS 1-49% vs. TPS ≥50%)

8.11 Compliance (Medication Adherence)

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

8.12 Extent of Exposure

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

9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.1 Investigational Product

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

Clinical Supplies will be provided by the Sponsor as summarized in Table 13.

Table 13 Product Descriptions

Product Name & Potency	Dosage Form
Pembrolizumab (MK-3475) 100 mg/ 4 mL	Solution for Infusion
Docetaxel 80 mg/ 4 mL	Solution for Infusion
Docetaxel 20 mg/ 0.5 mL	Solution for Infusion

All other supplies not indicated in Table 13 above will be provided centrally by the Sponsor or locally by the trial site, subsidiary or designee, depending on local country operational or regulatory requirements.

For any commercially available product that is provided by the trial site, subsidiary or designee every attempt will be made to source these supplies from a single lot/batch number. The trial site is responsible for record the lot number, manufacturer and expiry date of any locally purchased product as per local guidelines unless otherwise instructed by the Sponsor.

9.2 Packaging and Labeling Information

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

All supplies will be provided open label. pembrolizumab (MK-3475) and docetaxel will be provided as a kitted supply

9.3 Clinical Supplies Disclosure

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

9.4 Storage and Handling Requirements

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

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

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

9.5 Discard/Destruction/Returns and Reconciliation

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

9.6 Standard Policies

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

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

10.1 Confidentiality

10.1.1 Confidentiality of Data

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

10.1.2 Confidentiality of Subject Records

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

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

10.1.3 Confidentiality of Investigator Information

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

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

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

investigators. By signing this protocol, the investigator expressly consents to these uses and disclosures.

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

10.1.4 Confidentiality of IRB/IEC Information

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

10.2 Compliance with Financial Disclosure Requirements

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

The investigator/subinvestigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, commonly known as a financial disclosure form, provided by the Sponsor 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); and all applicable federal, state and local laws, rules and regulations relating to the conduct of the clinical trial.

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

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

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

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

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

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

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

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

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

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

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

10.4 Compliance with Trial Registration and Results Posting Requirements

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

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

10.5 Quality Management System

By signing this protocol, the Sponsor agrees to be responsible for implementing and maintaining a quality management system with written development procedures and

functional area standard operating procedures (SOPs) to ensure that trials are conducted and data are generated, documented, and reported in compliance with the protocol, accepted standards of Good Clinical Practice, and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the clinical trial.

10.6 Data Management

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

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

10.7 Publications

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

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

For multicenter trials, subsequent to the multicenter publication (or after public disclosure of the results online at www.clinicaltrials.gov if a multicenter manuscript is not planned), an

investigator and his/her colleagues may publish their data independently. In most cases, publication of individual trial site data does not add value to complete multicenter results, due to statistical concerns. In rare cases, publication of single trial site data prior to the main paper may be of value. Limitations of single trial site observations in a multicenter trial should always be described in such a manuscript.

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

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

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12.0 APPENDICES

12.1 Merck Code of Conduct for Clinical Trials

Merck*
Code of Conduct for Clinical Trials

I. Introduction

A. Purpose

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

B. Scope

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

II. Scientific Issues

A. Trial Conduct

1. Trial Design

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

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

2. Site Selection

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

3. Site Monitoring/Scientific Integrity

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

B. Publication and Authorship

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

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

III. Subject Protection

A. IRB/ERC review

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

B. Safety

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

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

C. Confidentiality

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

D. Genomic Research

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

IV. Financial Considerations

A. Payments to Investigators

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

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

B. Clinical Research Funding

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

C. Funding for Travel and Other Requests

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

V. Investigator Commitment

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

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

12.2 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 specimens collected in this trial as outlined in Section 7.1.3.3 – Future Biomedical Research will be used to study various causes for how subjects may respond to a drug/vaccine. Future biomedical research 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

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.

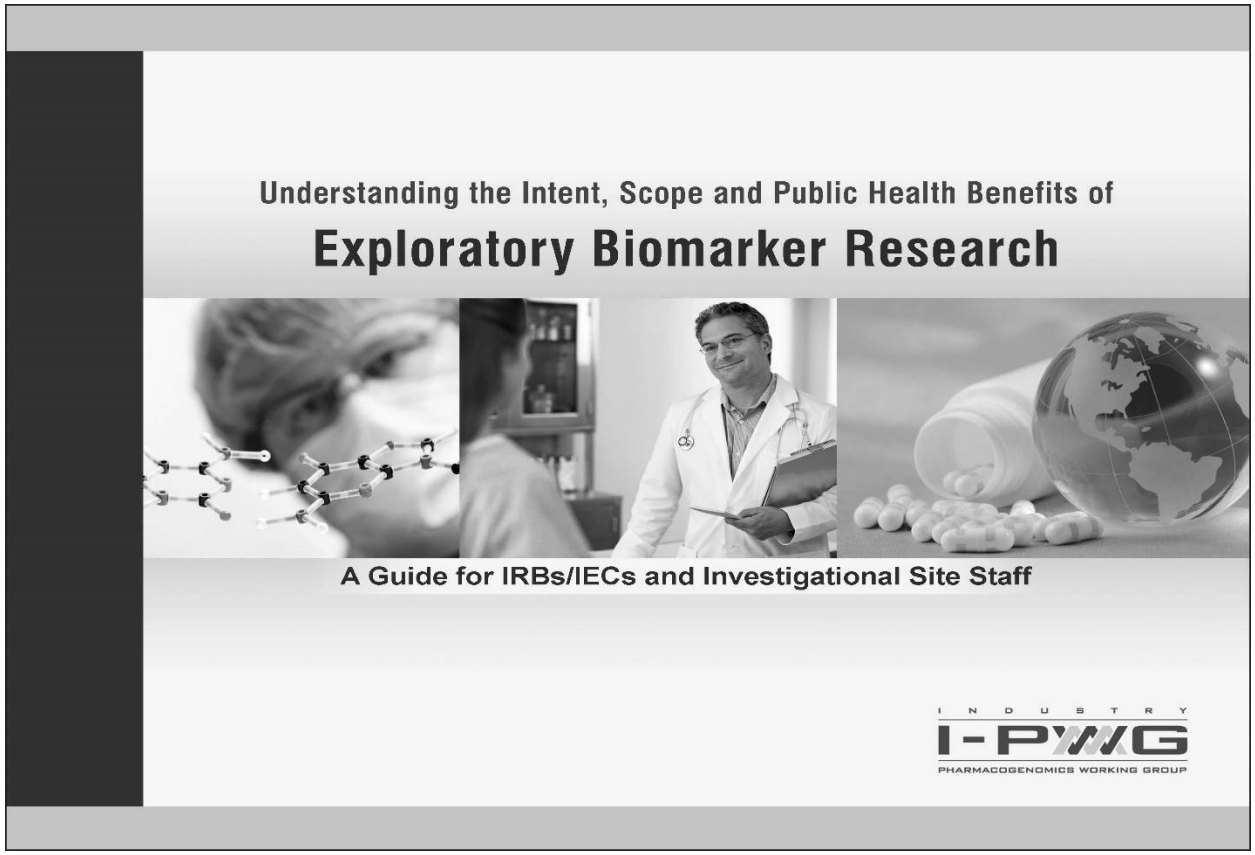
13. Questions

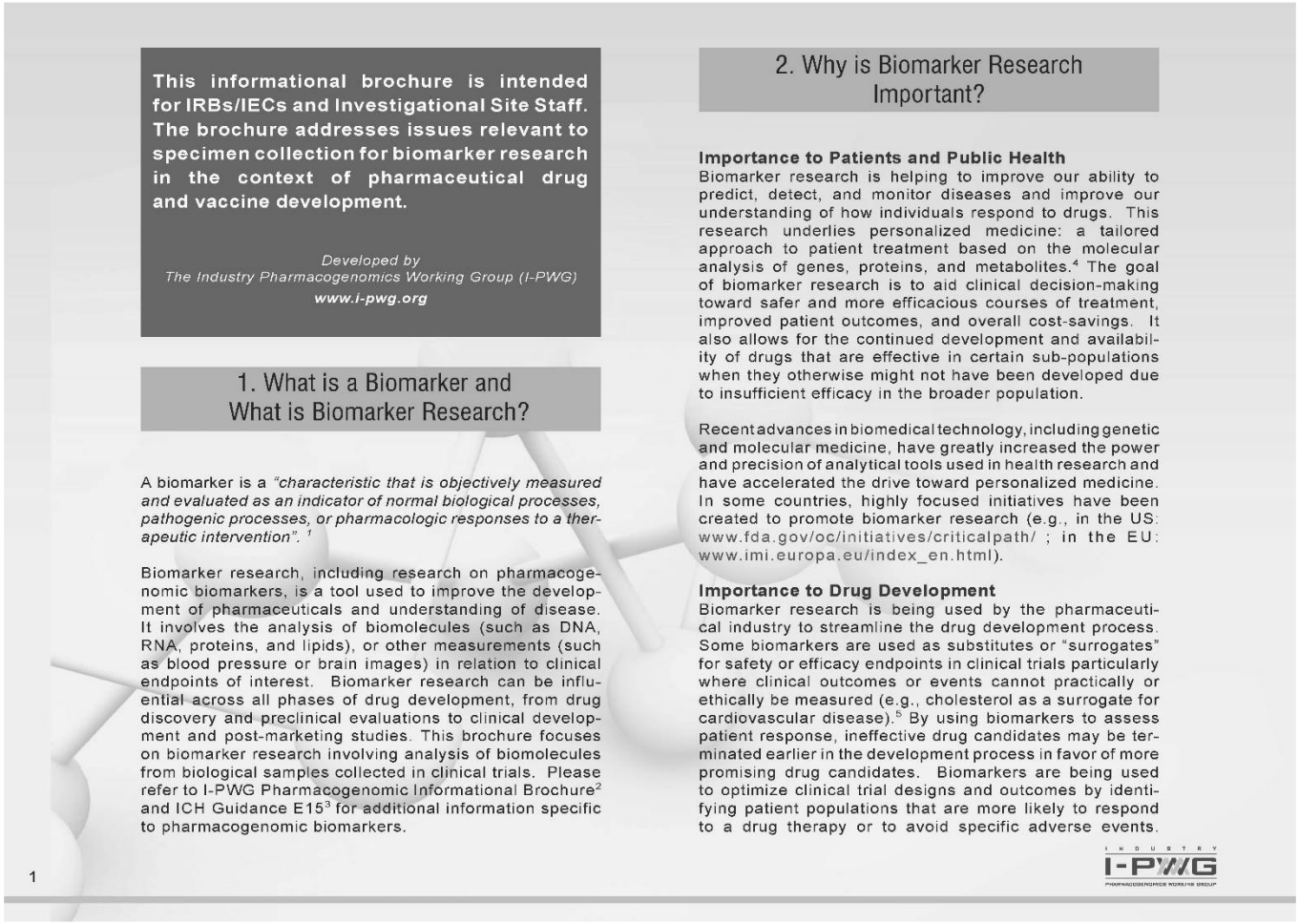
Any questions related to the future biomedical research should be e-mailed directly to clinical.specimen.management@merck.com.

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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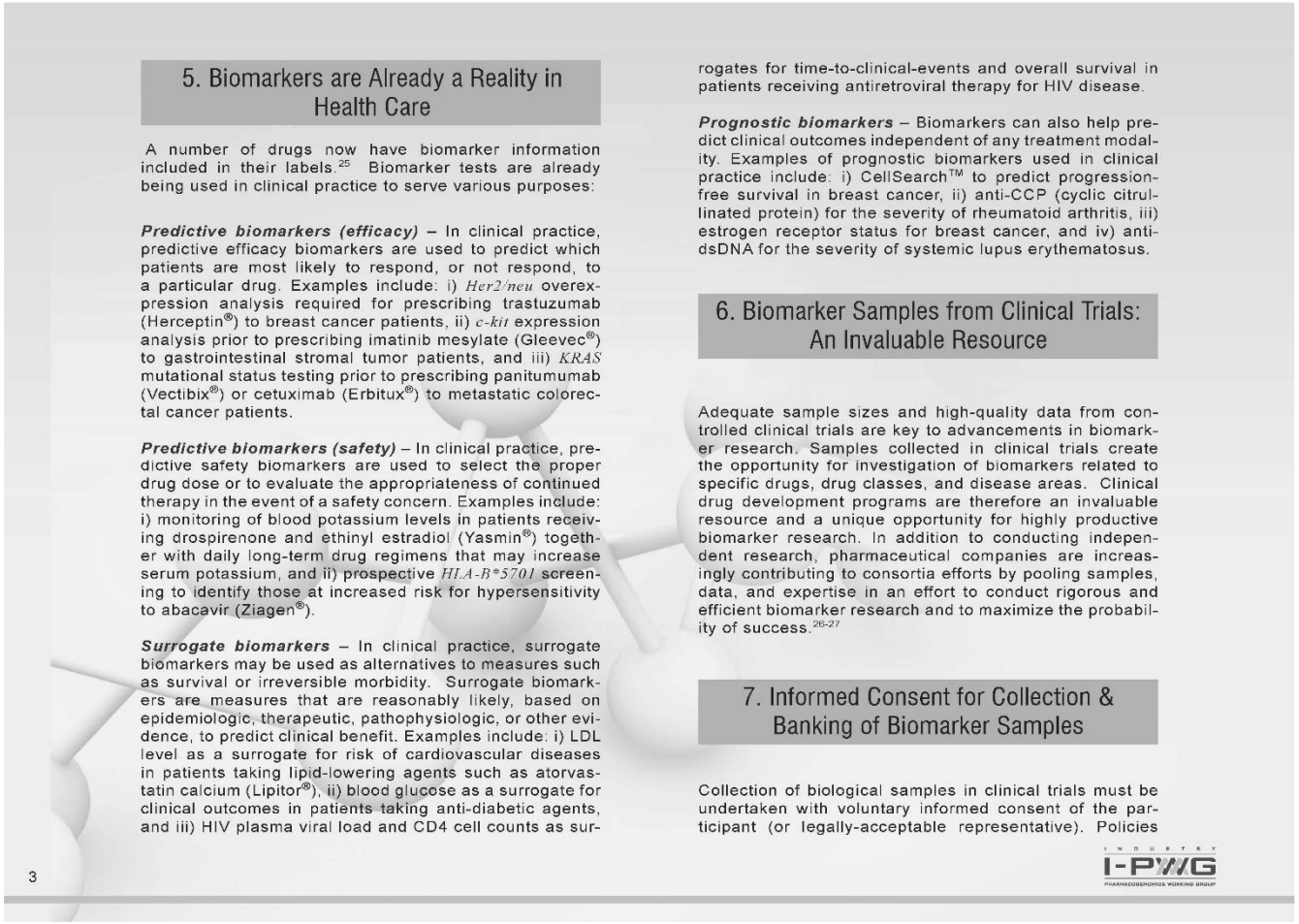

5. Biomarkers are Already a Reality in Health Care

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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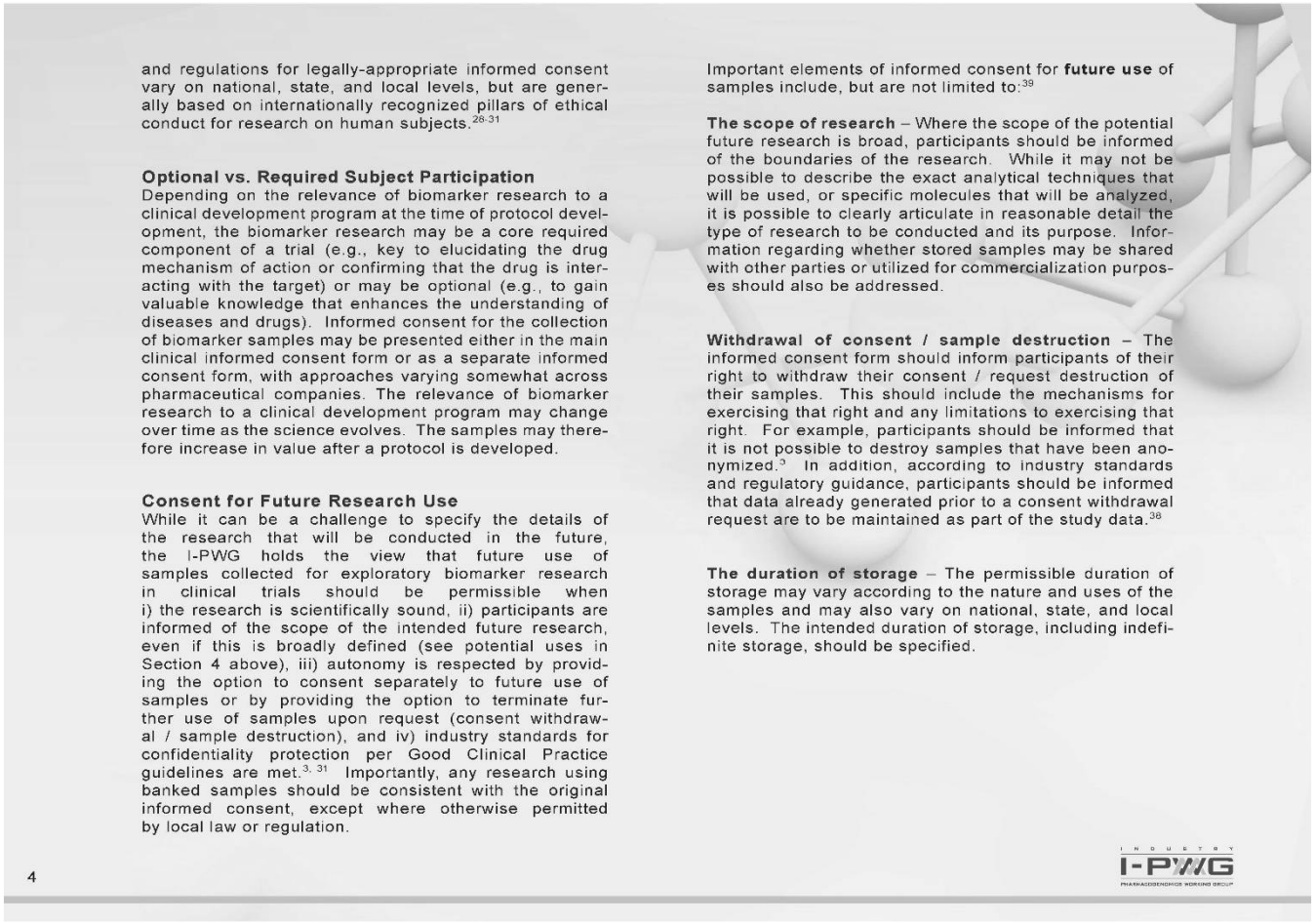

and regulations for legally-appropriate informed consent vary on national, state, and local levels, but are generally based on internationally recognized pillars of ethical conduct for research on human subjects.[26-31]

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.

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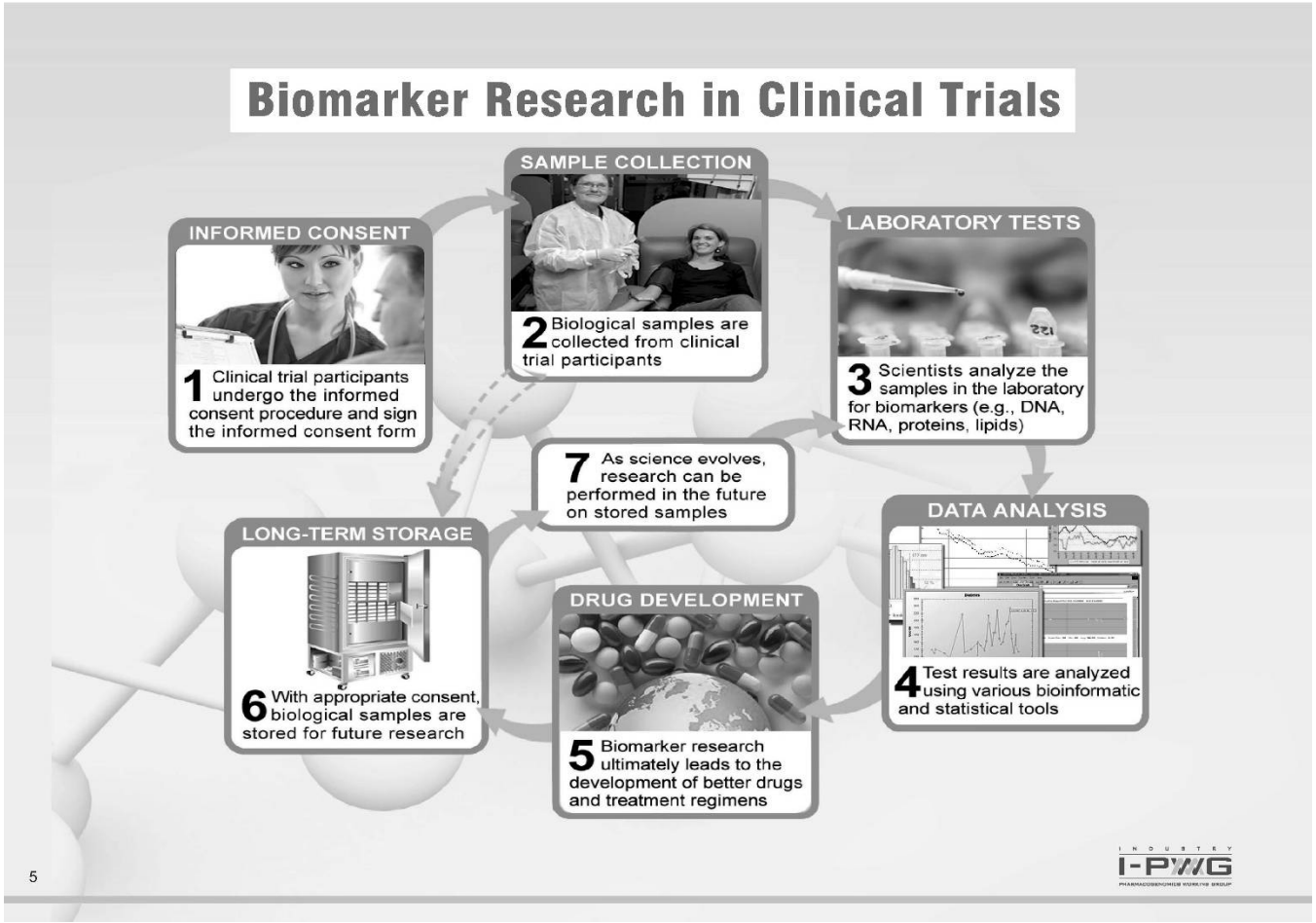
Biomarker Research in Clinical Trials
SAMPLE COLLECTION
2 Biological samples are collected from clinical trial participants
LABORATORY TESTS
3 Scientists analyze the samples in the laboratory for biomarkers (e.g., DNA, RNA, proteins, lipids)
INFORMED CONSENT
1 Clinical trial participants undergo the 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
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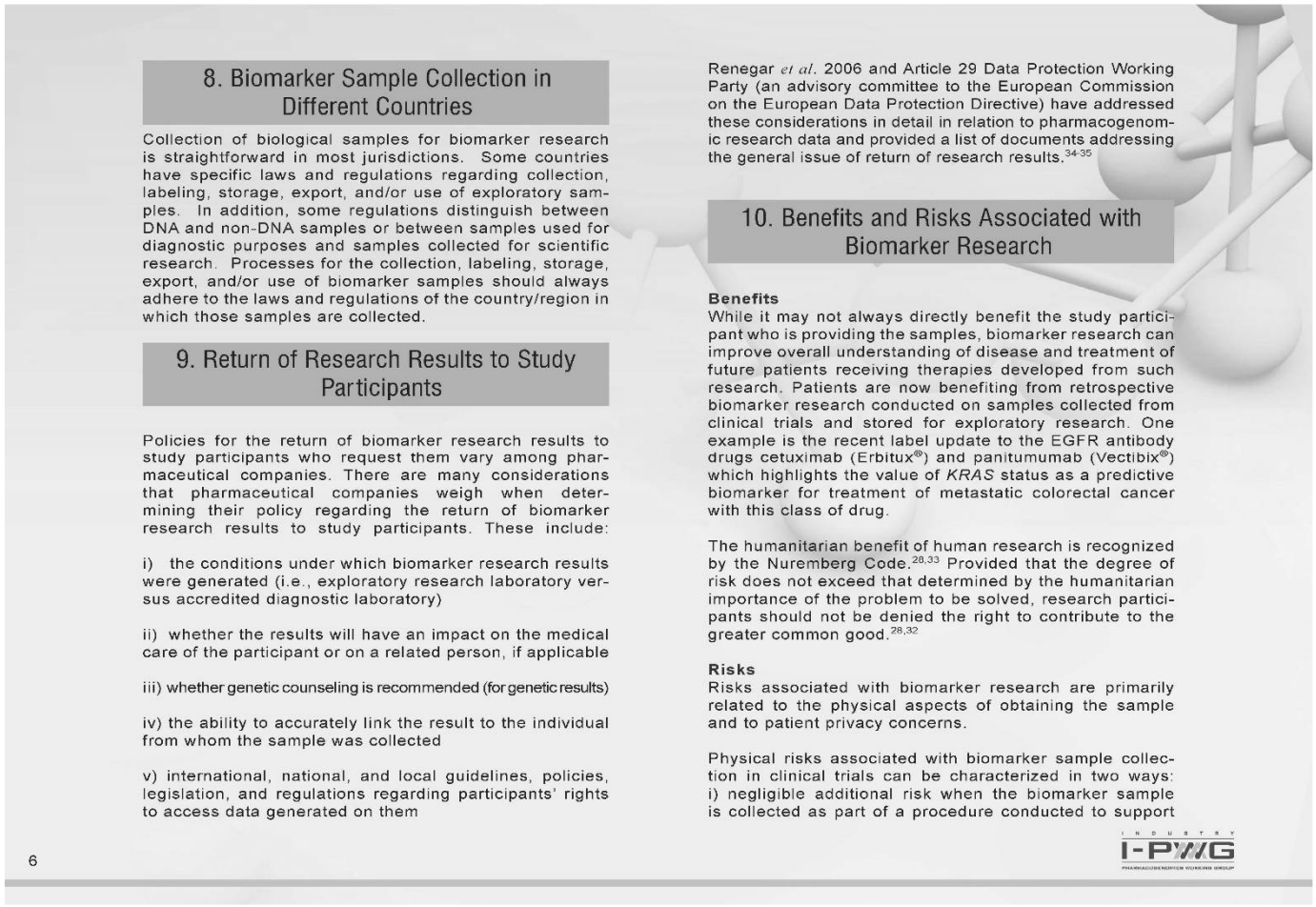
8. Biomarker Sample Collection in Different Countries
Collection of biological samples for biomarker research is straightforward in most jurisdictions. Some countries have specific laws and regulations regarding collection, labeling, storage, export, and/or use of exploratory samples. In addition, some 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
6
Renegar et al. 2006 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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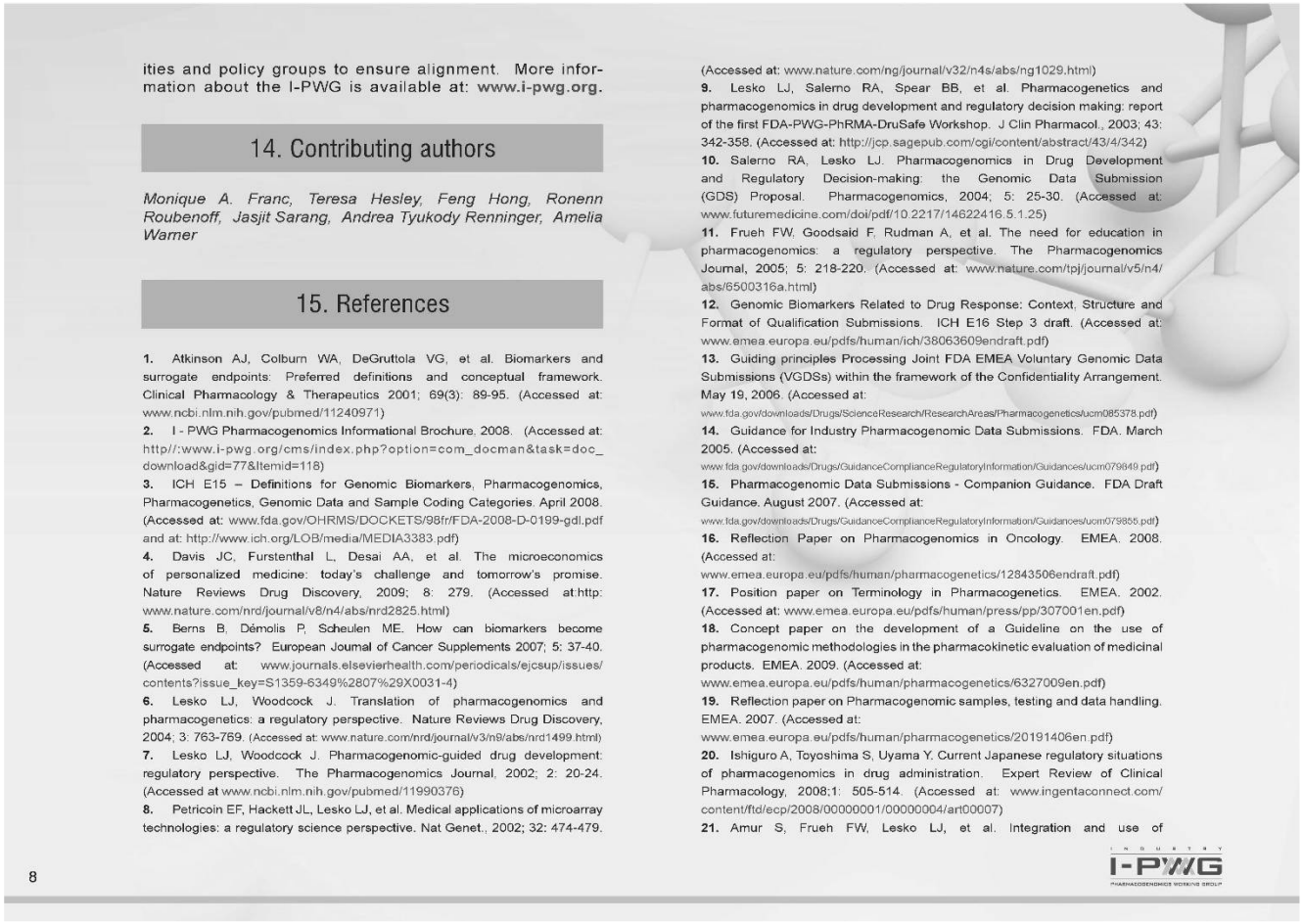

ities and policy groups to ensure alignment. More information about the I-PWG is available at: www.i-pwg.org.

14. Contributing authors

Monique A. Franc, Teresa Hesley, Feng Hong, Ronenn Roubenoff, Jasjit Sarang, Andrea Tyukody Renninger, Amelia Warner

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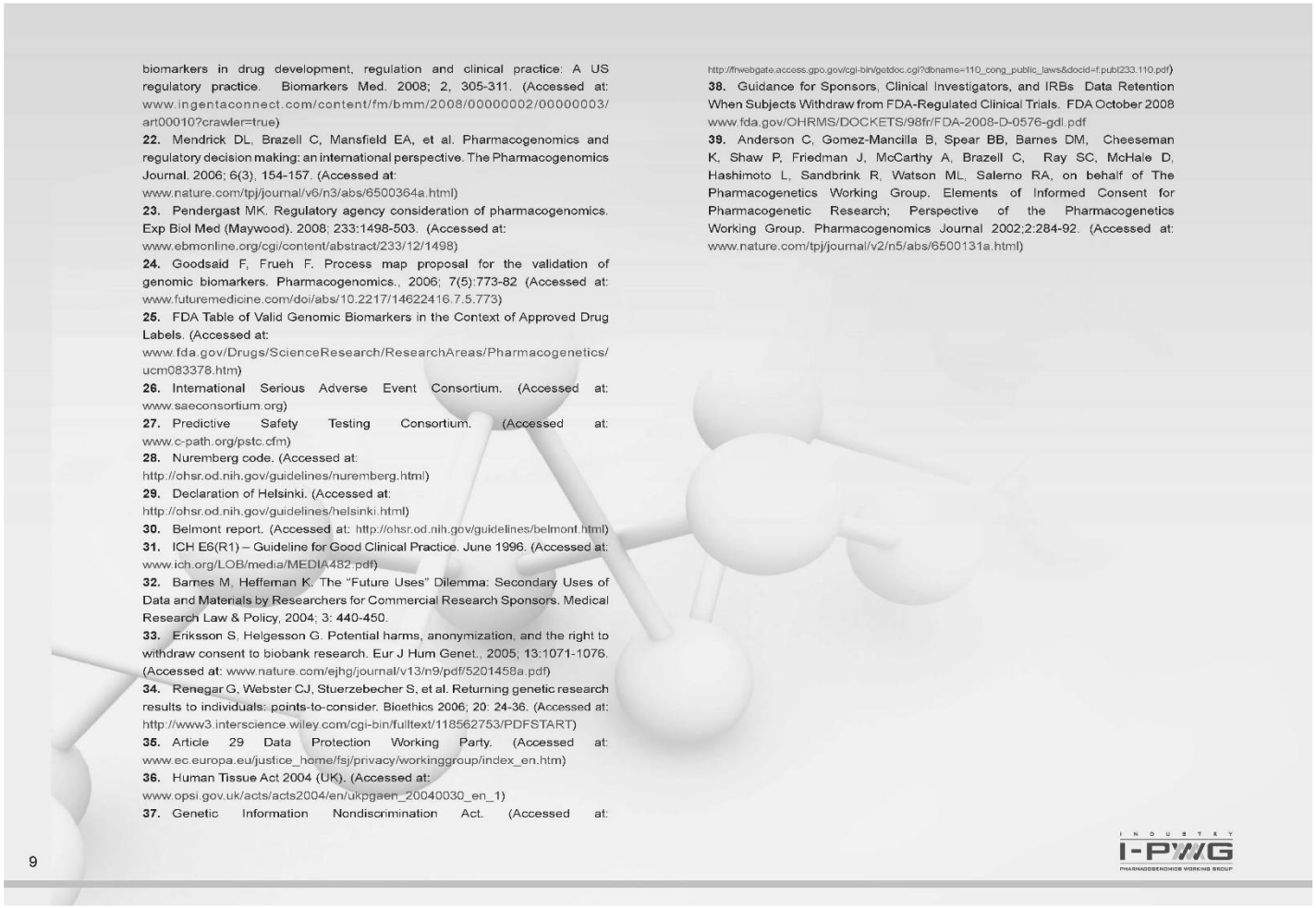

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12.4 ECOG Performance Status

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 MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5:649-55.* Eastern Cooperative Oncology Group, Robert Comis MD, Group Chair.

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

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

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

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

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

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

12.7 Strong Inhibitors of CYP3A4

Strong inhibitors of CYP3A4 include:

- Clarithromycin
- Indinavir
- Itraconazole
- Ketoconazole
- Nefazodone
- Nelfinavir
- Ritonavir
- Saquinavir

This appendix is not intended to be a comprehensive list of strong CYP3A4 inhibitors, but to provide a practical list of commonly prescribed medications that should be avoided in subjects participating in this study. Additional guidance for investigators on potential strong CYP3A4 inhibitors of clinical significance may be found at http://medicine.iupui.edu/flockhart/.

The web-based resources are intended as guidance for the investigators and not necessarily as a list of prohibited medications.

12.8 Contraceptive Guidance

12.8.1 Definitions

Women of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below):

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

- Premenarchal
- Premenopausal female with 1 of the following:
    - Documented hysterectomy
    - Documented bilateral salpingectomy
    - Documented bilateral oophorectomy

For individuals with permanent infertility due to an alternate medical cause other than the above (eg, Mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

- Postmenopausal female
    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
        - A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with two FSH measurements in the postmenopausal range is required.
    - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

12.8.2 Contraception Requirements

Contraceptives allowed during the study include[a]:
Highly Effective Contraceptive Methods That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
• Progestogen-only subdermal contraceptive implant[b,c] • Intrauterine hormone-releasing system (IUS)[c] • Non-hormonal IUD • Bilateral tubal occlusion
• Azoospermic partner (vasectomized or secondary to medical cause) This is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. A spermatogenesis cycle is approximately 90 days. Note: Documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
Sexual Abstinence • Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
[a] Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies. [b] If locally required, in accordance with CTFG guidelines, acceptable contraceptive implants are limited to those which inhibit ovulation. [c] IUS is a progestin releasing IUD. Note: The following are not acceptable methods of contraception: - Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and LAM. - Male condom with cap, diaphragm, or sponge with spermicide. - Male and female condom should not be used together (due to risk of failure with friction).

13.0 SIGNATURES

13.1 Sponsor's Representative

TYPED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	

13.2 Investigator

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

TYPED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	