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TITLE:

A Phase II/III Randomized Trial of Two Doses of MK-3475 (SCH900475) versus Docetaxel in Previously Treated Subjects with Non-Small Cell Lung Cancer

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SUMMARY OF CHANGES

PRIMARY REASON(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
1.0 2.1 2.2 2.3 4.2.2 5.8 6.3.1 7.1.5.4 7.1.5.5	Trial Summary Trial Design Trial Diagram Crossover for Subjects in Docetaxel Arm to MK-3475 200 mg arm Rationale for Dose Selection/ Regimen/ Modification Subject Withdrawal/Discontinuation Criteria Second Course Phase for MK-3475 200 mg Q3W Arm Second Course Phase Crossover for Subjects in the Docetaxel Arm to MK-3475 200 mg Arm	Treatment Group added: 200 mg every 3 weeks (Q3W) for retreatment and crossover subjects. Pembrolizumab dose for Second Course (Retreatment) and Crossover was changed to a fixed dose of 200 mg Q3W. Section 2.3 was deleted due to the change in dose for crossover subjects. Adaptive trial design discussion was expanded to explain the transition to the 200 mg fixed dose. Material from Section 4.2.2 was moved up to Section 2.1 for this reason.	The current approved standard of care for pembrolizumab treatment of non-small cell lung cancer (NSCLC) in the US is the fixed dose of 200 mg Q3W. This dose will be used for all subjects in the study who are in crossover or second course of treatment. The justification for using 200 mg Q3W fixed dose is provided in section 4.2.2.

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
2.1 6.1.1 6.3 6.4 7.1.4.1 7.1.5.3.2	Trial Design MK-3475 2 and 10 mg/kg Q3W and Docetaxel Arms Second Course Phase for MK-3475 200 mg Q3W Arm Second Course Post-Treatment Follow-up Phase Tumor Imaging Follow-up Visits	Radiographic imaging frequency during follow-up in the initial treatment phase was decreased after 54 week from every 9 weeks (63 ± 7 days) to every 12 weeks (84 ± 7 days) and in the Second Course Phase to every 12 weeks (84 ± 7 days).	To align with current follow-up schedule for pembrolizumab NSCLC studies.
6.2 7.1.5.3.3	Post-Treatment Follow-up Phase Survival Follow-up	Updated Survival Follow-up intervals from 2 months to 12 Weeks	To align with current follow-up schedule for pembrolizumab studies.

ADDITIONAL CHANGE(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
1.0 2.1	Trial Summary Trial Design	Added possible transition to an extension study following completion of KN010 treatment.	An extension study is planned, which may be available to subjects completing KN010.
1.0	Trial Summary – Estimated duration of the trial	Updated to 60 months.	To account for second course of treatment.
4.2.2	Rationale for Dose Selection/ Regimen/ Modification	Updated section to reflect current regulatory status of pembrolizumab	Section contained outdated material regarding dose selection.
5.2.1.2	Dose Modification	The dose modification guidelines for pembrolizumab were updated to add guidance for dose modification in the event of immune-related myocarditis, and to adjust guidance for all other immune-related AEs. Guidance for treatment of infusion reactions associated with pembrolizumab was moved to this section from Section 5.6.1	To reflect the current reference safety information and to align with the pembrolizumab standard template.

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
5.5.1 5.5.2	Acceptable Concomitant Medications Prohibited Concomitant Medications	Removed the prohibition of bisphosphonate or anti-RANKL mAb	To align with recent pembrolizumab NSCLC studies because this class of drug is commonly used to control symptoms of bone metastasis rather than tumor growth.
5.6.1	Supportive Care Guidelines	Section was updated to refer to Section 5.2.1.2 for guidance.	To align with the current pembrolizumab standard template.
5.6.3	Guidelines for Infusion Reaction	Moved to the Dose Modification Section	To align with the updated pembrolizumab standard template
5.7.2	Contraception	Updated to current pembrolizumab language	To align with the updated pembrolizumab standard template
5.7.3	Use in Pregnancy	Updated text to indicate that if a subject became pregnant, she would be removed from treatment rather than from the study.	To allow for safety follow-up.

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
5.8 6.1.1 7.1.5.4 Appendix 12.6	Subject Withdrawal/ Discontinuation Criteria Flow Chart for MK-3475 2 and 10 mg/kg Q3W and Docetaxel Arms (Footnote 17) Second Course Phase Immune-related Response Criteria	Changed timing for confirmatory scans from "at least 4 weeks" to "the next scheduled visit (ie, every 63 ± 7 days)".	Correction.
7.1.2.1 7.2.3.2	Adverse Event (AE) Monitoring Events of Clinical Interest	Removed reference to separate guidance on ECIs and events listed as ECIs that are no longer included in this category for reporting purposes.	Guidance is outdated and superseded by labeling.
7.1.3.1	Laboratory Safety Evaluations (Hematology, Chemistry, Urinalysis and Other)	Testing for Carbon Dioxide (CO_2 or bicarbonate) is no longer mandatory	Testing for Carbon Dioxide is not standard of care in all regions.
7.1.5.3	Post-Treatment Follow-up Phase	Removed 2 year limit of follow-up period and added specific instances when follow-up would end	Follow-up will continue until start of new antineoplastic therapy, disease progression, death, or is lost to follow-up, and is not limited to 2 years.

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
7.1.5.3.4	Survival Status	Updated text to indicate that contacts to determine survival may occur at more frequent intervals than scheduled.	To allow for obtaining current survival data and for such reasons as an updated analysis
7.1.5.4	Second Course Phase	Changed duration of treatment from “up to 12 months” to “up to 17 cycles (approximately 1 year)”	To align with standard pembrolizumab protocol.
7.1.5.4	Second Course Phase	Updated the inclusion and exclusion criteria section for the second course phase.	To facilitate determination of eligibility.
7.1.5.4	Second Course Phase	Updated the exclusion criterion for use of systemic steroids	To align with the pembrolizumab standard for lung cancer studies.

1.0 TRIAL SUMMARY

Abbreviated Title	MK-3475 vs. Docetaxel in Second-Line NSCLC
Trial Phase	Phase II/III
Clinical Indication	The treatment of subjects with non-small cell lung cancer (NSCLC) whose tumors are positive for PD-L1 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	MK-3475 10 mg/kg every 3 weeks MK-3475 2 mg/kg every 3 weeks Docetaxel 75 mg/m^2 every 3 weeks Second Course and Crossover MK-3475 200 mg every 3 weeks
Number of trial subjects	Approximately 920 subjects will be enrolled.
Estimated duration of trial	The sponsor estimates that the trial will require approximately 60 months from the time the first subject signs the informed consent until the last subject's last visit.
Duration of Participation	Each subject will participate in the trial from the time the subject signs the Informed Consent Form (ICF) through the final protocol-specified contact. After a screening phase of up to 42 days, eligible subjects will receive assigned treatment on Day 1 of each 3-week (Q3W) dosing cycle. Treatment with MK-3475 or docetaxel will continue for up to 35 cycles (approximately 2 years) of therapy have been administered, 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. MK-3475 treated subjects who attain a complete response may consider stopping trial treatment. These subjects will be eligible for re-treatment for up to 17 cycles (approximately 1 year) with MK-3475 after experiencing disease progression at the discretion of the investigator if they meet the criteria for re-treatment; this will be designated the Second Course phase. After the end of treatment, each subject will be followed for a minimum of 30 days for adverse event monitoring (serious adverse events will be collected for up to 90 days after the end of treatment). Subjects will have post-treatment follow-up for disease status, including initiating a non-study cancer treatment and experiencing disease progression, until death, withdrawing consent, or becoming lost to follow-up. **Following demonstration of a survival benefit, eligible subjects who were allocated to docetaxel, who experienced disease progression, will be permitted to cross-over to MK-3475 200 mg Q3W.** Once the subject has achieved the study objective or the study has ended, the subject will be discontinued from this study and will be enrolled in an extension study to continue protocol-defined assessments and treatment. Crossover patients who have not transitioned to pembrolizumab will be considered for the extension study on a case-by-case basis.
Randomization Ratio	1:1:1

2.0 TRIAL DESIGN

2.1 Trial Design

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.

This is a multi-center, worldwide, randomized, adaptively designed Phase II/III trial of intravenous (IV) MK-3475 at two dosing schedules versus docetaxel in subjects with non-small cell lung cancer (NSCLC) with PD-L1 positive tumors who have experienced disease progression after platinum-containing systemic therapy. Approximately 520-920 subjects will be enrolled in this trial to examine the efficacy compared to docetaxel in an enriched population. Subjects will be randomized in a 1:1:1 ratio to receive MK-3475 at 10 mg/kg every 3 weeks (Q3W), 2 mg/kg Q3W, or docetaxel at 75 mg/m^2 Q3W (Figure 1). Because this is an adaptively designed trial, the total number of patients randomized will depend upon demonstration of sufficient objective responses at interim analysis 1 in an MK-3475 arm in the stratum of subjects whose tumors test strongly positive for PD-L1. Assignment to MK-3475 or docetaxel will be unblinded. Subjects will be stratified by extent of tumoral PD-L1 expression (strongly positive vs. weakly positive), Eastern Cooperative Oncology Group (ECOG) Performance Scale (0 vs. 1), and geographic region of the enrolling site (East Asia vs. non-East Asia) prior to randomization.

Subjects will be evaluated with radiographic imaging to assess response to treatment every 9 weeks (63 ± 7 days) through Week 54, and every 12 weeks (84± 7 days) thereafter. Investigators will make all treatment-based decisions using the Immune-Related Response Criteria (irRC). All imaging obtained on study will be submitted for independent radiologists' review; they will assess the images using Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 for determination of overall response rate (ORR) and progression-free survival (PFS). Adverse events will be monitored throughout the trial and graded in severity according to the guidelines outlined in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Treatment with MK-3475 or docetaxel will continue for up to 35 cycles (approximately 2 years) of therapy have been administered, 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. MK-3475 treated subjects who attain an investigator-determined confirmed complete response (CR) per irRC may consider stopping trial treatment. These subjects will be eligible for re-treatment for up to 17 cycles (approximately 1 year) with MK-3475 200 mg IV Q3W after they have experienced radiographic disease progression at the discretion of the investigator according to the 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 of the primary endpoint in this trial. Subjects who were allocated to docetaxel who experience disease progression will be permitted to cross over to MK-3475 200 mg Q3W as long as Inclusion/Exclusion criteria defined in Section 7.1.5.5 are met.

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 will have post-treatment follow-up for disease status, including initiating a non-study cancer treatment and experiencing disease progression, until death, withdrawing consent, or becoming lost to follow-up.

The primary objectives of this trial are: 1) To compare the overall survival (OS) of previously-treated subjects with NSCLC in the strongly positive PD-L1 stratum treated with MK-3475 compared to docetaxel; 2) To compare progression-free survival (PFS) per RECIST 1.1 by independent radiologists' review of previously-treated subjects with NSCLC in the strongly positive PD-L1 stratum treated with MK-3475 compared to docetaxel; 3) To evaluate OS of previously-treated subjects with NSCLC whose tumors express PD-L1 and are treated with MK-3475 compared to docetaxel; 4) To evaluate PFS per RECIST 1.1 by independent radiologists' review of previously-treated subjects with NSCLC whose tumors express PD-L1 and are treated with MK-3475 compared to docetaxel, and; 5) Evaluate safety and tolerability profile of MK-3475 in previously-treated subjects with NSCLC in the strongly positive and overall PD-L1 stratums.

The study is considered to have met its primary objective in the primary population of subjects with overall positive or strongly positive PD-L1 expression if at least one MK-3475 arm is superior to docetaxel either in PFS or in OS at an interim analysis or the final analysis. Please refer to Sections 3.2 and 3.3 for a listing of secondary and exploratory objectives.

Participation in this trial will be dependent upon supplying tumor tissue from a newly obtained formalin-fixed specimen from locations not radiated prior to biopsy; no new systemic antineoplastic therapy may be administered between the PD-L1 biopsy and initiating study medication. The specimen will be evaluated at a central laboratory facility for expression status of PD-L1 in a prospective manner. Only subjects whose tumors express PD-L1 as determined by the central laboratory facility will be eligible for randomization in this study. Patients will be stratified into one of two groups (strongly positive or weakly positive) on the basis of these results.

This trial will use an adaptive design based on pre-specified criteria, using an independent, external Data Monitoring Committee (DMC) to monitor safety and efficacy. These analyses will be carried out in the strongly positive PD-L1 stratum first and then possibly in the overall PD-L1 positive population, with the former being primary analysis population. Two formal interim analyses based on the data from the randomized cohort will occur during the conduct of this trial. The first interim analysis will be triggered after 120 subjects in the strongly positive PD-L1 stratum have completed a minimum of 3 months of follow-up. The primary objective of this analysis is to stop the study for futility or to discontinue one MK-3475 arm if it is less efficacious than the other MK-3475 arm based on ORR in the strongly positive PD-L1 stratum.

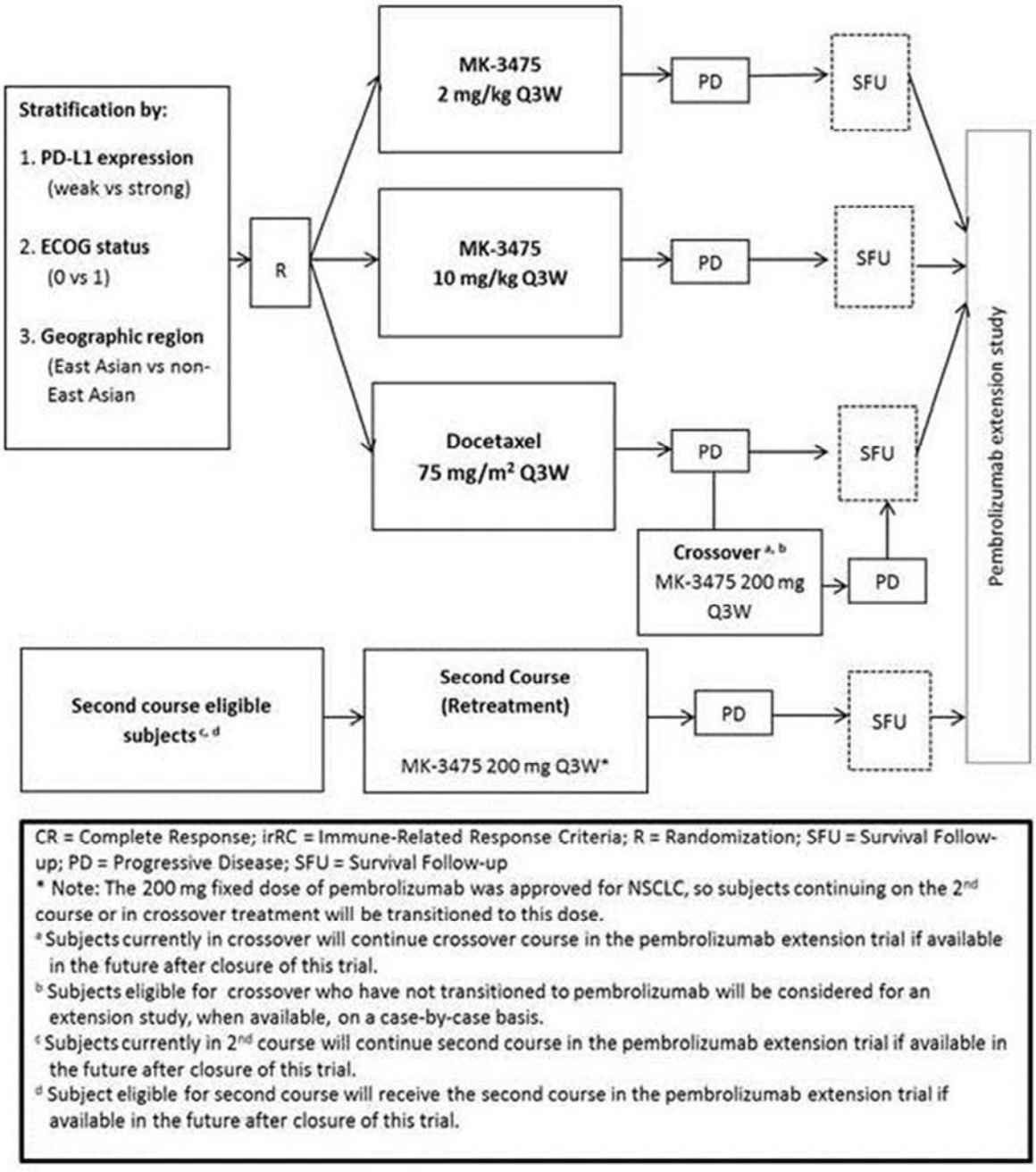
The second interim analysis is expected to occur after approximately 175 events of progression per RECIST 1.1 by independent radiologists' review, and around 120 OS events have occurred across three arms in the strongly positive PD-L1 stratum (approximately 123

progression events and 84 OS events between one MK-3475 arm and docetaxel arm under the alternative hypothesis). The purpose of the second interim analysis is to demonstrate superiority of MK-3475 in PFS and OS in the strongly positive PD-L1 stratum and the overall population of subjects with positive PD-L1 expressions. In addition, the trial may be stopped early at the recommendation of the DMC if the risk/benefit ratio to the trial population as a whole is unacceptable. Details are described in Section 8.0 – Statistical Analysis Plan.

If one MK-3475 dose is dropped due to lack of efficacy, per the investigator's discretion the subjects can continue to be treated with MK-3475 on the other dose. The efficacy and safety data from these patients will not be used in the primary analysis, but will be used in supportive analyses.

2.2 Trial Diagram

The trial design is depicted in Figure 1.



CR = Complete Response; irRC = Immune-Related Response Criteria; R = Randomization; SFU = Survival Follow-up; PD = Progressive Disease; SFU = Survival Follow-up

* Note: The 200 mg fixed dose of pembrolizumab was approved for NSCLC, so subjects continuing on the 2nd course or in crossover treatment will be transitioned to this dose.

[a] Subjects currently in crossover will continue crossover course in the pembrolizumab extension trial if available in the future after closure of this trial.

[b] Subjects eligible for crossover who have not transitioned to pembrolizumab will be considered for an extension study, when available, on a case-by-case basis.

[c] Subjects currently in 2nd course will continue second course in the pembrolizumab extension trial if available in the future after closure of this trial.

[d] Subject eligible for second course will receive the second course in the pembrolizumab extension trial if available in the future after closure of this trial.

Figure 1 Trial Design

3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

3.1 Primary Objective(s) & Hypothesis(es)

1) Objective: To compare the overall survival (OS) of previously-treated subjects with NSCLC in the strongly positive PD-L1 stratum treated with MK-3475 compared to docetaxel.

   Hypothesis: MK-3475 prolongs OS in previously-treated subjects with NSCLC in the strongly positive PD-L1 stratum compared to docetaxel.

2) Objective: To compare progression-free survival (PFS) per RECIST 1.1 by independent radiologists' review of previously-treated subjects with NSCLC in the strongly positive PD-L1 stratum treated with MK-3475 compared to docetaxel.

   Hypothesis: MK-3475 prolongs PFS per RECIST 1.1 by independent radiologists' review in previously-treated subjects with NSCLC in the strongly positive PD-L1 stratum compared to docetaxel.

3) Objective: To evaluate OS of previously-treated subjects with NSCLC whose tumors express PD-L1 and are treated with MK-3475 compared to docetaxel.

   Hypothesis: MK-3475 prolongs OS in previously-treated subjects with NSCLC whose tumors express PD-L1 compared to docetaxel.

4) Objective: To evaluate PFS per RECIST 1.1 by independent radiologists' review of previously-treated subjects with NSCLC whose tumors express PD-L1 and are treated with MK-3475 compared to docetaxel.

   Hypothesis: MK-3475 prolongs PFS per RECIST 1.1 by independent radiologists' review in previously-treated subjects with NSCLC whose tumors express PD-L1 compared to docetaxel.

5) Objective: Evaluate safety and tolerability profile of MK-3475 in previously-treated subjects with NSCLC in the strongly positive and overall PD-L1 stratums.

The study is considered to have met its primary objective if at least one MK-3475 arm is superior to docetaxel either in PFS or in OS at an interim analysis or the final analysis in the overall study population whose tumors express PD-L1 or the strongly positive PD-L1 stratum.

3.2 Secondary Objective(s) & Hypothesis(es)

1) Objective: To evaluate overall response rate (ORR) per RECIST 1.1 by independent radiologists' review in previously-treated subjects with NSCLC in the strongly positive PD-L1 stratum and in overall study population whose tumors express PD-L1 treated with MK-3475 compared to docetaxel.

2) Objective: To evaluate response duration per RECIST 1.1 by independent radiologists' review in previously-treated subjects with NSCLC in the strongly positive PD-L1 stratum and in overall study population treated with MK-3475 compared to docetaxel.

3.3 Exploratory Objectives

1) Objective: To evaluate PFS per immune-related response criteria (irRC) by investigators' review in previously-treated subjects with NSCLC in the strongly positive PD-L1 stratum and in overall study population whose tumors express PD-L1 treated with MK-3475 compared to docetaxel.

2) Objective: To evaluate ORR per irRC by investigators' review in previously-treated subjects with NSCLC in the strongly positive PD-L1 stratum and in overall study population treated with MK-3475 compared to docetaxel.

3) Objective: To evaluate response duration per immune-related response criteria (irRC) by investigators' review in previously-treated subjects with NSCLC in the strongly positive PD-L1 stratum and in overall study population whose tumors express PD-L1 treated with MK-3475 compared to docetaxel.

4) Objective: To evaluate the influence of age of tumor specimen (archival vs. new) submitted for PD-L1 analysis on the primary endpoints of progression-free survival and overall survival.

5) Objective: To evaluate tumor volumetric changes of previously-treated subjects with NSCLC in the strongly positive PD-L1 stratum treated with MK-3475 compared to docetaxel.

6) Objective: To explore the correlation of tumor volumetric changes with OS in previously-treated subjects with NSCLC in the strongly positive PD-L1 stratum with MK-3475 compared to docetaxel.

7) Objective: To evaluate changes in health-related quality-of-life assessments from baseline in previously-treated subjects with NSCLC in the strongly positive PD-L1 stratum treated with MK-3475 compared to docetaxel using the EORTC QLQ C-30 and EORTC QLQ LC-13.

8) Objective: To characterize utilities in previously-treated subjects with NSCLC in the strongly positive PD-L1 stratum treated with MK-3475 compared to docetaxel using the EuroQoL EQ-5D.

9) Objective: Characterize healthcare resource utilization in previously-treated subjects with NSCLC in the strongly positive PD-L1 stratum treated with MK-3475 compared to docetaxel.

4.0 BACKGROUND & RATIONALE

4.1 Background

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

4.1.1 Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance function in controlling outgrowth of neoplastic transformations has been known for decades [1]. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T cells/FoxP3+ regulatory T-cells (T-regs) correlates with improved prognosis and long-term survival in solid malignancies, such as ovarian, colorectal, and pancreatic cancer; hepatocellular carcinoma; malignant melanoma; and renal cell carcinoma. Tumor-infiltrating lymphocytes can be expanded ex vivo and reinfused, inducing durable objective tumor responses in cancers such as melanoma [2] [3].

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an immunoglobulin (Ig) superfamily member related to cluster of differentiation 28 (CD28) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) that has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD L1 and/or PD-L2) [4] [5].

The structure of murine PD-1 has been resolved [6]. PD-1 and its family members are type I transmembrane glycoproteins containing an Ig-variable–type (IgV type) domain responsible for ligand binding and a cytoplasmic tail responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif, and an immunoreceptor tyrosine-based switch motif. Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases, SHP-1 and SHP-2, to the immunoreceptor tyrosine-based switch motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3 zeta (CD3ζ), protein kinase C-theta (PKCθ), and zeta-chain-associated protein kinase (ZAP70), which are involved in the CD3 T-cell signaling cascade [5] [7] [8] [9]. The mechanism by which PD-1 down-modulates T cell responses is similar to, but distinct from, that of CTLA-4, because both molecules regulate an overlapping set of signaling proteins [10] [11].

Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. High expression of PD-L1 on tumor cells (and to a lesser extent of PD-L2) has been found to correlate with poor prognosis and survival in various cancer types, including RCC [12], pancreatic carcinoma [13], hepatocellular carcinoma [14], and ovarian carcinoma [15]. Furthermore, PD-1 has been suggested to regulate tumor-specific T-cell expansion in subjects with MEL [16].

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

Several means of quantitatively scoring PD-L1 expression were evaluated using ROC curve analyses and assessment of positive and negative predictive values of potential strong/weak cutoffs. Based on the analyses performed in Protocol 001, a proportion score with a cutoff of 50% or more of tumor cells staining for PD-L1 was selected as an optimal strong/weak cutoff. The best overall response rate of patients with strongly positive tumors in the training set by investigator-assessed irRC was 46% (95% CI: 30%, 61%) compared to 8% (95% CI: 3%, 15%) in patients with weakly positive/negative tumors. The best overall response rate of patients with strongly positive tumors in the training set by independently-assessed RECIST was 37% (95% CI: 22%, 53%) compared to 11% (95% CI: 6%, 20%) in patients with weakly positive/negative tumors.

4.1.2 Information on Other Trial-Related Therapy

Three products are approved in most major markets to treat patients who have failed first-line therapy, docetaxel, erlotinib, and pemetrexed. Two studies, TAX317 and TAX320, formed the basis of approval of docetaxel for this indication. TAX317 demonstrated superior overall survival for docetaxel at 75 mg/m^2 Q3W compared to best supportive care (risk ratio 0.56, log rank test p-value 0.01). The median overall survival in the TAX317 trial was 7.5 months for docetaxel compared to 4.6 months for best supportive care. The 1-year survival rate was 37% for docetaxel compared to 12% for best supportive care (p-value $\leq$ 0.05). The response rate for docetaxel was 5.5% (95% CI: 1.1, 15.1) based on WHO response criteria [13]. Similarly, TAX320 also demonstrated a superior 1-year survival rate for docetaxel at 75 mg/m2 of 30% compared to 20% in the control arm of vinorelbine or ifosfamide (p-value $\leq$ 0.05). However, the risk ratio for overall survival was not statistically significant in the TAX320 study (risk ratio 0.8s, log rank test p-value 0.13). The median overall survival in the TAX320 trial was 5.7 months for docetaxel versus 5.6 months for the control. The response rate for docetaxel in TAX320 was 5.7% (95% CI: 2.3%, 11.3%) based on WHO response criteria [17]. Thus, docetaxel was approved as an acceptable second-line therapy for patients with NSCLC.

Pemetrexed is also an approved second-line agent for NSCLC based on a trial attempting to demonstrate non-inferiority to docetaxel (median OS: 8.3 months pemetrexed vs. 7.9 months docetaxel, HR 0.99, p-value=0.226) [18]. Another study also demonstrated that pemetrexed provides an improvement in OS when administered in a first-line setting in combination with cisplatin compared to treatment with cisplatin/gemcitabine in patients with non-squamous (adenocarcinoma: n=847, 12.6 vs. 10.9 months, respectively; HR=0.84; 95% CI, 0.71 to 0.99; P=.03; large-cell carcinoma: n = 153, 10.4 v 6.7 months, respectively; HR=0.67; 95% CI, 0.48 to 0.96; P=.03; nonsquamous: n=1,000, 11.8 v 10.4 months, respectively; HR = 0.81; 95% CI, 0.70 to 0.94; P = .005) [19]. Pemetrexed's approved indication is limited to patients with NSCLC with non-squamous histology by both the FDA and EMA and is commonly used as part of first-line therapy in patients with non-squamous NSCLC. So it is used less commonly as a second-line therapy.

Erlotinib is an inappropriate second-line therapy for patients with a good performance status who do not have an EGFR mutation. More recently, the TAILOR trial has reported the median PFS for patients EGFR wild type is better when they are treated with docetaxel as opposed to erlotinib (HR 0.70 with 95% CI 0.53-0.94; p = 0.016) [20]. So, docetaxel is the most appropriate comparator in this second-line trial of patients with progressive NSCLC after a platinum-containing regimen. The most common adverse reactions for patients treated with docetaxel are infections, neutropenia, anemia, febrile neutropenia, hypersensitivity, thrombocytopenia, neuropathy, dysgeusia, dyspnea, constipation, anorexia, nail disorders, fluid retention, asthenia, pain, nausea, diarrhea, vomiting, mucositis, alopecia, skin reactions, and myalgia [17] [21] [22] [23].

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

While docetaxel is an accepted second-line standard of care for patients with NSCLC, the objective response rate is about 5-10%, median progression-free survival is about 3 months, and the median overall survival is about 7.5 months [17] [21] [22]. Improvements in OS are needed since no one with progressive NSCLC is cured.

A large surgical series of resected NSCLC specimens revealed that about 25% of squamous and adenocarcinoma have tumor infiltrating lymphocytes (TILs) present [24]. These TILs often contain CD8+ T cells [24]. The presence of increased CD8+ cells in the tumor sets the stage for an immune-based response against the tumor if inhibition of the immune system can be abrogated. Indeed, in a study of ipilimumab, an anti-CTLA4 monoclonal antibody, combined with first-line carboplatin and paclitaxel, a post-hoc subset analysis identified an improvement in OS that favored patients with squamous histology compared to placebo plus carboplatin and paclitaxel (HR 0.48 [95% CI 0.22-1.03]). Results were not as favorable for patients with nonsquamous histology (HR 1.17 [95% CI 0.74-1.86]). These findings have led to the initiation of a Phase III trial in the same population with ipilimumab.

Please see the end of Section 4.1.1 which discusses the classification of tumors as strongly positive or weakly positive based on PD-L1 scoring. This study will compare monotherapy MK-3475 with standard of care docetaxel in patients with NSCLC. Overall survival and PFS in the strongly positive PD-L1 subpopulation are the primary endpoints of the trial, and are accepted regulatory endpoints for this disease.

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. Patients in the strongly positive PD-L1 subset who receive 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 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 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 MK-3475 as they might be from docetaxel.

4.2.2 Rationale for Dose Selection/Regimen/Modification

In the first in human study (Protocol number 001, refer to IB), which treated a variety of tumor types, 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). Dose level 10 mg/kg Q3W was evaluated in previously treated patients with NSCLC in Part C of Protocol 001.

In this study, pembrolizumab 2 mg/kg Q3W, pembrolizumab 10 mg/kg Q3W, and docetaxel 75 mg/m^2 Q3W have been evaluated in 1033 subjects through response or progression. The final analysis was carried out when approximately 200 deaths occurred across the 3 study arms in the TPS≥50% stratum. The study's final analysis results revealed that both MK-3475 2 mg/kg and 10 mg/kg arms were associated with superior overall survival compared to the docetaxel arm in the PD-L1 strongly positive stratum as well as in the overall study population.

Based on the positive outcome of the OS analysis, subjects in the docetaxel arm, who experienced disease progression, had the opportunity to crossover to MK-3475 2 mg/kg Q3W treatment arm. This was the initial dose approved by the Food and Drug Administration (FDA) for treatment of melanoma subjects. However, current clinical trials evaluating pembrolizumab are using a fixed dose of 200 mg Q3W. Therefore, the dose of pembrolizumab for the second course and crossover portions of this trial will now be 200 mg Q3W.

The use of a fixed dose is based on PK findings summarized below.

The PK profile of pembrolizumab is consistent with that of other humanized monoclonal antibodies, which typically have a low clearance and a limited volume of distribution. A population PK model, which characterized the influence of body weight and other subject covariates on exposure using available data from 1139 subjects (from Keynote-001 and Keynote-002) has been performed. The majority of these subjects (1077; 94.6%) had advanced melanoma. The distribution of exposures from the 200 mg fixed dose were predicted to considerably overlap those obtained with the 2 mg/kg dose, and importantly, maintained individual subject exposures within the exposure range established in melanoma as associated with maximal clinical response. This comparison also demonstrated that the 200 mg Q3W regimen provided no substantive differences in PK variability (range of the distribution of individual exposures) as seen with weight-based dosing.

In translating to other solid tumor indications, similarly flat exposure-response relationships for efficacy and safety as observed in subjects with melanoma can be expected, as the antitumor effect of pembrolizumab is driven through immune system activation rather than

through a direct interaction with tumor cells, rendering it independent of the specific tumor type. In addition, available PK results in subjects with melanoma, NSCLC, and other solid tumor types support a lack of meaningful difference in PK exposures obtained at tested doses among tumor types.

4.2.3 Rationale for Endpoints

4.2.3.1 Efficacy Endpoints

4.2.3.1.1 Primary

Overall Survival is the gold standard endpoint to demonstrate superiority of antineoplastic therapy. Progression free survival 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. RECIST 1.1 will be used to determine the dates of progression as this methodology is accepted by regulatory authorities. Because the treatment assignment is unblinded regarding MK-3475 vs. docetaxel, images will be read by independent radiologists blinded to treatment assignment to minimize bias in the response assessments.

4.2.3.1.2 Secondary

Importantly, PFS will also be assessed by irRC as determined by the investigators. ORR will be calculated by both methodologies, in addition to the duration of response. All main analyses will be performed in the strongly positive PD-L1 stratum.

An analysis that includes all patients will be conducted for primary and secondary endpoints if the study is positive for that endpoint in the strongly positive PD-L1 stratum.

4.2.3.2 Patient Reported Outcomes

The EORTC QLQ-C30, EORTC QLQ-LC13, and EQ5D are not pure efficacy or safety endpoints because they are affected by both disease progression and treatment tolerability.

4.2.3.2.1 eEORTC QLQ-C30 and EORTC QLQ-LC13

The EORTC-QLQC30 is the most widely used cancer specific 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 [25] This instrument is translated and validated into more than 80 languages.

In combining with EORTC QLQ C-30, 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) [26]. The EORTC QLQ-C30 and QLQ-LC13 are the most frequently utilized and reported patient-

reported outcome measures in lung cancer clinical trials [27] [28]. The reliability, validity and practicality of these instruments have been reported [26] [29].

4.2.3.2.2 eEuroQol EQ-5D

The eEuroQol-5D (eEQ-5D) is a standardized instrument for use as a measure of health outcome. The eEQ-5D will provide data for use in economic models and analyses including developing health utilities or 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 eEQ-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 eEQ-5D will always be completed by patients first before completing the eEORTC QLQ C-30 and EORTC LC-13.

4.2.3.3 Future Biomedical Research

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

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, and/or to ensure that subjects receive the correct dose of the correct drug at the correct time. The details of this Future Biomedical Research sub-trial are presented in Section 12.2 - Collection and Management of Specimens for Future Biomedical Research. Additional informational material for institutional review boards/ethics committees (IRBs/ERCs) and investigational site staff is provided in Section 12.3.

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

Male/Female subjects with NSCLC whose tumors express PD-L1 who have experienced disease progression after at least a platinum-containing systemic therapy of at least 18 years of age 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/assent for the trial.

2) Be ≥18 years of age on day of signing informed consent.

3) Have a life expectancy of at least 3 months.

4) Have a histologically or cytologically confirmed diagnosis of non-small cell lung cancer (NSCLC) and have at least one measurable lesion as defined by RECIST 1.1. The target lesion(s) should also have bi-dimensional measurability for irRC evaluation on study.

5) Have experienced investigator determined radiographic progression per RECIST 1.1 of NSCLC after treatment with at least two cycles of a platinum-containing doublet for stage IIIB/IV or recurrent disease. The site's study team must have reviewed pre-trial images that are of diagnostic quality from at least 2 dates to determine that radiographic progression has occurred per RECIST 1.1 following initiation of the first-line platinum-containing doublet. A platinum-containing doublet is defined as a platinum-based cytotoxic systemic agent administered in the same cycle as another cytotoxic systemic chemotherapeutic agent. The central imaging vendor must have received these scans and have confirmed that they are of acceptable diagnostic quality prior to randomization in this trial for a possible retrospective analysis of this eligibility criterion. The central vendor will not be confirming eligibility prior to randomization. Completion of treatment with a platinum-containing doublet as adjuvant therapy within one year of signing informed consent will satisfy the prior treatment requirement.

    a. Subjects with an EGFR sensitizing mutation must also be able to demonstrate progression of disease on the EGFR tyrosine kinase inhibitor (either erlotinib, gefitinib, or afatinib) in a similar manner to that above for the platinum-containing doublet. Radiographic images that demonstrate progression after initiation of the EGFR tyrosine kinase inhibitor therapy and after initiation of the platinum-containing doublet must also be submitted similarly for subjects with an EGFR sensitizing mutation prior to randomization. Subjects with an EGFR sensitizing mutation may have been treated previously with the

tyrosine kinase inhibitor separately from the platinum-containing doublet; the order of treatment does not matter, but progression of disease as determined by RECIST 1.1 must be demonstrable for both regimens. An exception to this rule is the patient whose NSCLC tumor has an EGFR sensitizing mutation who receives four cycles of a platinum doublet, does not experience progression of disease, and begins therapy with an EGFR tyrosine kinase inhibitor as a maintenance therapy within 28 days of the last administration of the platinum doublet chemotherapy. For this patient, only one set of images demonstrating progression on the EGFR tyrosine kinase inhibitor is required for submission to the independent imaging vendor for the patient to be eligible.

b. Subjects with an ALK translocation must also be able to demonstrate progression of disease on crizotinib in a similar manner to that above for the platinum-containing doublet. Radiographic images that demonstrate progression after initiation of crizotinib and after initiation of the platinum-containing doublet must also be submitted similarly for subjects with an ALK translocation prior to randomization. Subjects with an ALK translocation may have been treated previously with the tyrosine kinase inhibitor separately from the platinum-containing doublet; the order of treatment does not matter, but progression of disease as determined by RECIST 1.1 must be demonstrable for both regimens.

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

7) 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 transfusions for 4 weeks
Renal	
Creatinine OR calculated creatinine clearance (CrCl)[a] (GFR can also be used in place of creatinine or CrCl)	≤1.5 X upper limit of normal (ULN) OR ≥60 mL/min for subjects with creatinine levels > 1.5 X institutional ULN
Hepatic	
Total bilirubin	≤ ULN
AST (SGOT) and ALT (SGPT)	≤ 1.5 X ULN
Alkaline Phosphatase	≤ 2.5 X ULN
Endocrine	
Thyroid stimulating hormone (TSH)	Within normal limits[b]
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT)	≤1.5 X ULN unless the subject is receiving anticoagulant therapy
Activated Partial Thromboplastin Time (aPTT)	≤1.5 X ULN unless the subject is receiving anticoagulant therapy

[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 (or free T3) and free T4 are within the normal limits.

8) Have provided tissue for PD-L1 biomarker analysis from a newly obtained formalin-fixed tumor tissue from a recent biopsy of a tumor lesion not previously irradiated; no systemic antineoplastic therapy may be administered between the PD-L1 biopsy and initiating study medication. Although patients using tyrosine kinase inhibitors prior to treatment on this protocol may continue using these until it is time to begin the appropriate wash out period for these medications. For patients in whom obtaining a new tumor biopsy will be medically inappropriate, the investigator may appeal to the Sponsor's study clinical director, and if there is agreement, 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. Needle or excisional biopsies, or resected tissue is required.

    a. Investigators must be able to produce the source documentation of the EGFR mutation status or ALK translocation status. If unable to test for these molecular changes, formalin-fixed paraffin-embedded tumor tissue of any age should be submitted to a central laboratory designated by the Sponsor for such testing. Subjects will not be randomized until EGFR mutation and ALK translocation status is available in source documentation at the site.

b. 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.

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

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

9) Have a PD-L1 positive (either strongly or weakly) tumor as determined by IHC at a central laboratory. 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.

10) 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.

11) Female subject of childbearing potential has a negative urine or serum pregnancy test. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. The serum pregnancy test must be negative for the subject to be eligible.

12) Female subjects may be enrolled in the trial if they are:

- of non-childbearing potential which is defined as:

  - a female patient ≥ 45 years of age and has not had menses for greater than 2 years,

  - a female who is amenorrheic for < 2 years without a hysterectomy and oophorectomy and an FSH value in the postmenopausal range upon pretrial (screening) evaluation,

    and/or

  - a female who is status post hysterectomy, oophorectomy or tubal ligation. Documented hysterectomy or oophorectomy must be confirmed with medical records of the actual procedure or confirmed by an ultrasound. Tubal ligation must be confirmed with medical records of the actual procedure otherwise the

subject will be excluded. Information must be captured appropriately within the site's source documents.

- of childbearing potential who are willing to use either 2 adequate barrier methods or a barrier method plus a hormonal method of contraception to prevent pregnancy, or to abstain from heterosexual activity throughout the trial, starting with the screening visit (Visit 1) through 120 days after the last dose of MK-3475. Such methods of contraception, or abstinence from heterosexual activity, are required from the screening visit (Visit 1) through 180 days after the last dose of docetaxel. Please see Section 5.7.2 for a list of acceptable birth control methods.

13) Male subjects with a female partner(s) of child-bearing potential must agree to use 2 adequate barrier methods or a barrier method plus a hormonal method of contraception to prevent pregnancy, or to abstain from heterosexual activity throughout the trial starting with the screening visit (Visit 1) through 120 days after the last dose of MK-3475 is received. Such methods of contraception, or abstinence from heterosexual activity, are required from the screening visit (Visit 1) through 180 days after the last dose of docetaxel. If their partner is pregnant, males must agree to use a condom and no additional method of contraception is required for the pregnant partner.

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

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 using an investigational device within 30 days of the first dose of trial treatment. The 30 day window should be applied to the last dose of an antineoplastic investigational agent or last use of an investigational device with antineoplastic intent.

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).

5) Has received prior systemic cytotoxic chemotherapy, antineoplastic biological therapy (e.g., cetuximab), 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 tyrosine kinase inhibitor therapy or completed palliative radiotherapy 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, anti-CD137, or anti-Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways) or has participated in another MK-3475 clinical trial.

7) Has a known history of prior malignancy except if the patient has undergone potentially curative therapy with no evidence of that disease recurrence for 5 years since initiation of that therapy.

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

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 4 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. The two brain MRIs that were used to make the determination of stable disease must be submitted to the central imaging vendor, preferably while the subject is undergoing screening. These images should be submitted retrospectively for subjects that have already been randomized.

9) Has an active autoimmune disease, or a documented history of autoimmune disease, or a syndrome that requires systemic steroids or immunosuppressive agents. Subjects with vitiligo or resolved childhood asthma/atopy would be exception to this rule. Subjects that require inhaled steroid or local steroid injections will not be excluded from the study. Subjects with hypothyroidism not from autoimmune disease and stable on hormone replacement will not be excluded from the study.

10) Has had an allogeneic tissue/solid organ transplant.

11) Has interstitial lung disease or a history of pneumonitis that required oral or intravenous glucocorticoids to assist with management. Lymphangitic spread of the NSCLC is not exclusionary.

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) Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the screening visit (Visit 1) through 120 days after the last dose of MK-3475 or 180 days after the last dose of docetaxel.

20) Subjects that require treatment with a strong inhibitor of CYP3A4 will be excluded. They 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.

5.2 Trial Treatments

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

Treatments to be used in this trial are outlined below in Table 2 and Section 5.2.2

Table 2 Trial Treatments

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period
MK-3475	2 mg/kg	Q3W	IV infusion	Day 1 of each cycle
MK-3475	10 mg/kg	Q3W	IV infusion	Day 1 of each cycle
MK-3475	200 mg	Q3W	IV infusion	Day 1 of each cycle
Docetaxel	75 mg/m^2	Q3W	IV infusion	Day 1 of each cycle
If one dose arm is dropped due to lack of efficacy, per the investigator's discretion the subjects can continue to be treated with the other dose. The MK-3475 dosing interval may be increased due to toxicity as described in Section 5.2.1.2. In the midst of the study, the preparation of MK-3475 will change from a lyophilized preparation to a liquid preparation.				

5.2.1 Dose Selection/Modification

5.2.1.1 Dose Selection

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 MK-3475 infusion solution will be based on the subject's weight in kilograms (kg). Details on the dose calculation, preparation and administration are provided in the Procedures Manual.

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

5.2.1.2 Dose Modification

Docetaxel

Refer to approved product label for subjects receiving docetaxel.

MK-3475

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

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

General instructions:

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

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

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

Immune-related AEs	Toxicity grade or conditions (CTCAEv4.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
Myocarditis	Grade 1 or 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
All other immune-related AEs	Intolerable/ persistent Grade 2	Withhold	• Based on type and severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3	Withhold or discontinue based on the type of event. Events that require discontinuation include and not limited to: Guillain-Barre Syndrome, encephalitis		
	Grade 4 or recurrent Grade 3	Permanently discontinue		

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

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

Dose modification and toxicity management of infusion reactions related to pembrolizumab

Pembrolizumab may cause severe or life-threatening infusion reactions, including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab associated infusion reaction are provided in Table 4.

Table 4 Pembrolizumab Infusion Reaction Dose Modification and Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable, in the opinion of the investigator.	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Increase monitoring of vital signs, as medically indicated, until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (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 study drug treatment	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of analgesic).

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 study drug treatment.**	No subsequent dosing
Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE) at http://ctep.cancer.gov		

Other allowed dose interruption for pembrolizumab

Pembrolizumab may be interrupted for situations other than treatment-related AEs such as medical / surgical events or logistical reasons not related to study therapy. 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 except for the post-infusion PK sample time points listed in the Trial Flow Chart. Trial treatment may be administered up to 3 days after Day 1 of each cycle due to administrative reasons only.

The specific time of MK-3475 administration (e.g., time of the week for first administration; time of the day for each administration) should take into consideration PK sampling time points and study visit procedures.

All trial treatments will be administered on an out-patient basis.

5.2.2.1 MK-3475

MK-3475 will be administered as a 30 minute IV infusion Q3W (treatment cycle intervals may be increased due to toxicity as described in Section 5.2.1.2). 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). Therefore, start and stop times of infusion is required for PN010 so that appropriate monitoring of protocol specified duration time may be performed.

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

5.2.2.2 Docetaxel

Docetaxel 75 mg/m^2 will be administered as an IV infusion over 1 hour every Q3W. All patients 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 irRC approximately 9 weeks 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

5.2.3.1 Treatment Trial Blinding

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.

5.2.3.2 Biomarker Trial Blinding

A double-blind technique will be used for the level PD-L1 positivity of randomized subjects. The subject, the investigator and Sponsor personnel or delegate(s) who are involved in the treatment or clinical evaluation of the subjects are unaware of the PD-L1 status.

5.3 Randomization or Treatment Allocation

Randomization will occur centrally using an IVRS/IXRS There are 3 treatment arms. Subjects will be assigned randomized treatment in an 1:1:1 ratio to MK-3475 10 mg/kg Q3W, MK-3475 2 mg/kg Q3W, or docetaxel 75 mg/m^2 Q3W. If one MK-3475 dose is

dropped during the trial then all subsequent subjects will be randomized in a 1:1 ratio to the other dose of MK-3475 or docetaxel in an unblinded fashion.

5.4 Stratification

Randomization will be stratified according to the following factors:

- Extent of tumoral PD-L1 expression (Strongly positive vs. Weakly positive)
- Geographic region of the enrolling site (East Asia vs. non-East Asia)
- Eastern Cooperative Oncology Group (ECOG) Performance Scale (0 vs. 1).

5.5 Concomitant Medications (allowed & prohibited)

Drugs specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. Listed below are some specific restrictions for concomitant therapy use during the course of the trial. If there is a clinical indication for one of these or other medications specifically prohibited during the trial, discontinuation from trial therapy may be required. The investigator should discuss any questions regarding this with the local Clinical Monitor. The final decision on any supportive therapy rests with the investigator and/or the subject's primary physician. However, the decision to continue the subject on trial therapy 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 the community standards of medical care. All concomitant medication will be recorded on the case report form (CRF) including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date will also be included on the CRF.

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 MK-3475.
- Radiation therapy (Treatment and Second Course Phases).
- 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.
- Glucocorticoids for any purpose other than adverse event management or for use as a pre-medication for docetaxel.
- Strong inhibitors of the CYP3A4 enzymes (a common list of such agents may be found in Appendix 12.8). **Subjects in the crossover phase and second course are allowed to receive strong inhibitors of the CYP3A4 enzymes.**

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. Pre-medication with corticosteroid for side effect prophylaxis for docetaxel is permitted.

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. Refer to approved product label for subjects receiving docetaxel.

MK-3475

Subjects should receive appropriate supportive care measures, as deemed necessary by the treating investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined along with the dose modification guidelines in Section 5.2.1.2, (Table 3). Where appropriate, these guidelines include the use of oral or IV treatment with corticosteroids, as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or

bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab.

Note: If after the evaluation of the event, it is determined not to be related to pembrolizumab, the investigator does not need to follow the treatment guidance. Refer to Table 3 in Section 5.2.1.2 for guidelines regarding dose modification and supportive care.

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

5.7 Diet/Activity/Other Considerations

5.7.1 Diet

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

5.7.2 Contraception

MK-3475 may have adverse effects on a fetus in utero. Furthermore, it is not known if MK-3475 has transient adverse effects on the composition of sperm. Docetaxel can cause fetal harm if administered to pregnant women. Therefore, non-pregnant, non-breast-feeding women may be enrolled if they are considered of non-reproductive potential. For this trial, male subjects will be considered to be of non-reproductive potential if they have azoospermia (whether due to having had a vasectomy or due to an underlying medical condition).

Female subjects will be considered of non-reproductive potential if they meet one of the following criteria:

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

- She had a hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy or bilateral tubal ligation/occlusion, at least 6 weeks prior to screening.

- She has a congenital or an acquired condition that prevents childbearing.

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

- Practice abstinence from heterosexual activity.

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

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

Acceptable methods of contraception are[‡]:

- Single method (one of the following is acceptable):
  - o Intrauterine device (IUD)
  - o Vasectomy of a female subject's male partner
  - o Contraceptive rod implanted into the skin
- Combination method (requires use of two of the following):
  - o Diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide)
  - o Cervical cap with spermicide (nulliparous women only)
  - o Contraceptive sponge (nulliparous women only)
  - o Male condom or female condom (cannot be used together)
  - o Hormonal contraceptive: oral contraceptive pill (estrogen/progestin pill or progestin-only pill), contraceptive skin patch, vaginal contraceptive ring, or subcutaneous contraceptive injection

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

Subjects should be informed that taking the trial medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the trial. In order to participate in the trial, subjects of childbearing potential must adhere to the contraception requirement (described above) from the day of trial medication initiation (or 14 days prior to the initiation of trial medication for oral contraception) throughout the trial period up to 120 days after the last dose of pembrolizumab and up to 180 days after last dose of docetaxel. If there is any question that a subject of childbearing potential will not reliably comply with the requirements for contraception, that subject should not be entered into the trial.

5.7.3 Use in Pregnancy

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

5.7.4 Use in Nursing Women

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

5.8 Subject Withdrawal/Discontinuation Criteria

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

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

- The subject or legal representative (such as a parent or legal guardian) withdraws consent.

For subjects participating in the optional crossover phase the same rules of discontinuation will apply. Subjects will continue treatment until disease progression occurs or as outlined in Section 7.1.5.6.

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

- The subject or legal representative (such as a parent or legal guardian) withdraws consent
- Documented disease progression

Note: If a subject has confirmed progression of disease by irRC, 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 the next scheduled time point (i.e., every 63 +/- 7 days). Clinical Stability is defined as:

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

2. No decline in ECOG performance status.

3. 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 uninterrupted delivery of MK-3475 every 3 weeks and no documented progression of disease, or 35 administrations of study medication, whichever is later
- Intercurrent illness that prevents further administration of treatment
- Investigator's decision to withdraw the subject
- The subject has a confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements
- The subject is lost to follow-up
- Administrative reasons

If an MK-3475 treated subject attains an investigator-determined confirmed CR according to irRC, has been treated for at least six months with MK-3475, and has at least two treatments with MK-3475 beyond the date when the initial CR was declared, the subject and investigator may consider stopping therapy with MK-3475. Subjects who discontinue MK-3475 after attaining a CR (or have experienced a PR or SD after 35 administrations of MK-3475) and then experience radiographic disease progression according to irRC will be eligible for re-treatment with MK-3475 in the Second Course Phase at the discretion of the investigator as described in Section 7.1.5.4.

Docetaxel may be discontinued when a subject has received the maximum number of cycles permitted by the local regulatory authority.

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, becoming lost to follow-up or entering the Second Course Phase. After documented disease progression each subject will either move into the Second Course Phase or be followed for overall survival until death or withdrawal of consent.

5.9 Subject Replacement Strategy

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

5.10 Beginning and End of the Trial

The overall trial begins when the first subject signs the informed consent form. The overall trial ends when the last subject completes the last trial visit, discontinues from the trial or is lost to follow-up (i.e., the subject is unable to be contacted by the investigator). Upon study completion, subjects receiving ongoing treatment will be discontinued from this study and enrolled in a pembrolizumab extension study, when available. Subjects who are eligible for crossover to pembrolizumab will be considered for the extension study on a case-by-case basis.

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 futility at the recommendation of the DMC if the first interim analysis results show neither MK-3475 dose schedule is superior to docetaxel.

2. The trial will be stopped early for efficacy at the recommendation of the DMC if the second interim analysis results show MK-3475 is superior to docetaxel in OS.

3. The trial will be stopped early at the recommendation of the DMC if the risk/benefit ratio to the trial population as a whole is unacceptable.

Statistical criteria for stopping the trial are provided in Section 8.0 – Statistical Analysis Plan and the DMC charter.

Enrollment will not be halted during either of 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 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. Possible choices of subsequent therapy include:

- Docetaxel
- Erlotinib
- Gemcitabine
- Vinorelbine

The exact subsequent treatment(s) used will be at the discretion of the investigator and determined by the interests of the subject.

Subjects randomized to docetaxel who experience progression of their cancer are not permitted to enroll in MK-3475 PN001 subsequently.

6.0 TRIAL FLOW CHART

6.1 Treatment Phase

6.1.1 MK-3475 2 and 10 mg/kg Q3W and Docetaxel Arms

	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 to 35	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	
Clinical Procedures / Assessments																
Review Adverse Events [6, 7]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Full Physical Examination	X				X			X			X			X	X[21]	
Directed Physical Examination		X	X	X		X	X		X	X		X	X		X[21]	X
Vital Signs and Weight [8]	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 to 35	Discontinuation Visit
Scheduling Window (Days):[2]			± 3	± 3	± 3	± 3	± 3	±3	± 3	±3	±3	± 3	± 3	± 3	± 3	
12-Lead ECG	X															
ECOG Performance Status	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pulmonary Function Testing[22]	X															
Laboratory Procedures / Assessments: analysis performed by local laboratory																
Pregnancy Test - Urine or Serum β-HCG [9]	X															
PT/INR and aPTT [10]	X [11]															
CBC with Differential[12]	X [11]		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Comprehensive Chemistry Panel[12]	X [11]		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis[12]	X [11]					X				X				X	X[13]	X
T3/**FT3**, FT4 and TSH [12, 14]	X [11]		**X**		**X**		**X**		**X**		**X**		**X**		X [13]	X
ALK Translocation Testing[23]	X															
EGFR Mutation Testing[23]	X															
Laboratory Procedures / Assessments: analysis performed by central laboratory																
Blood for Future Biomedical Research[15] (optional)		X														
Efficacy Measurements																
Tumor Imaging [16, 17]	X				X			X			X			X	X[16]	X
Patient Reported Outcomes (PRO)																
EuroQol EQ-5D [18]		X	X	X		X				X				X[13]		X
EORTC QLQ-C30[18]		X	X	X		X				X				X[13]		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 to 35	Discontinuation Visit
Scheduling Window (Days):[2]			± 3	± 3	± 3	± 3	± 3	±3	± 3	±3	±3	± 3	± 3	± 3	± 3	
EORTC QLQ LC-13 [18]		X	X	X		X				X				X[13]		X
Health Economic Assessment [18]			X	X		X				X				X[13]		X
Tumor Biopsies / Archival Tissue Collection																
Tumor Tissue Collection	X[19]			X[20]		X[20]				X[20]						

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 MK-3475 treatment cycle interval may be increased due to toxicity according to the dose modification guidelines provided in Section 5.2.1.2. 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 first dose of trial treatment through Week 54, and then every 12 weeks (84± 7 days) 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 Section 12.2.

5 Prior medications - Record all medications taken within 30 days of Visit 1 and all treatments for a prior cancer other than NSCLC even if taken greater than 30 days prior to Visit 1 (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 Section 7.2.

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 All AEs of unknown etiology associated with trial treatment exposure should be evaluated to determine if it is possibly an ECI. (See the separate guidance document in the administrative binder regarding identification, evaluation and management of AEs of a potential immunologic etiology).

8 Vital signs to include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at Visit 1 only.

9 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.

10 Coagulation factors (PT/INR and aPTT) should be monitored closely throughout the trial for any subject receiving anticoagulant therapy.

11 Laboratory tests for screening are to be performed within 10 days prior to the first dose of trial treatment. See Section 7.1.3 for details regarding laboratory tests.

12 After Cycle 1, lab samples can be collected up to 48 hours 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.

13 Perform every 4 cycles after Cycle 13; perform thyroid testing every other cycle.

14 Thyroid function tests will be performed by a central laboratory only if the local laboratory is unable to perform this service.

15 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 Section 12.2.

	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 to 35	Discontinuation Visit
Scheduling Window (Days):[2]			± 3	± 3	± 3	± 3	± 3	±3	± 3	±3	±3	± 3	± 3	± 3	± 3	

16 The initial tumor imaging will be performed within 30 days prior to the first dose of trial treatment. Scans performed as part of routine clinical management are acceptable for use as the screening scan if they are of diagnostic quality and performed within 30 days prior to the first dose of trial treatment. On-study imaging will be performed every 9 weeks (63 ± 7 days) after the first dose of trial treatment through Week 54, and then every 12 weeks (84± 7 days), or more frequently if clinically indicated. The timing for imaging studies should follow calendar days and should not be adjusted for delays in cycle starts or extension of MK-3475 cycle frequencies. The same imaging technique should be used in a subject throughout the trial. Local reading (investigator assessment with site radiology reading) will be used to determine eligibility and for subject management; Sponsor will collect radiological assessments for a potential retrospective analysis by a central vendor. The processes for image collection and transmission to the central vendor are in the investigator Imaging Operations Manual (IIOM).

17 After the first documentation of progression (if the subject is clinically stable) or response per irRC repeat imaging for confirmation is required. Confirmatory imaging scan should be performed at the next scheduled time point (i.e., every 63 +/- 7 days).

18 PROs are to be administered by trained site personnel and completed electronically by subjects in the following order: EuroQol EQ-5D first, then EORTC QLQ C-30, and lastly the EORTC LC-13. It is most relevant and strongly recommended that ePROs are administered prior to study drug administration, adverse event evaluation and disease status notification. HEA will be completed by qualified site personnel after the subject completes all other questionnaires.

19 Tumor tissue for biomarker analysis from an archival tissue sample (acceptable for EGFR and ALK testing) or newly obtained formalin fixed tumor tissue from a recent biopsy of a tumor lesion not previously irradiated (required for PD-L1 determination; acceptable for EGFR and ALK testing) must be provided and received by the central vendor before randomization. No systemic antineoplastic therapy may have been received by the patient between the time of the biopsy for PD-L1 testing and the first administration of study medication. 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.

20 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. Detailed instructions for tissue collection, processing and shipment are provided in the Procedures Manual. Patients who agree to undergo these additional, optional tumor biopsies while receiving MK-3475 may not have them under CT-guidance.

21 Perform a full physical examination every 3 cycles after Cycle 12. Otherwise, perform a directed physical examination the day of the study treatment visit.

22 Pulmonary function tests should include an assessment of forced vital capacity, forced expiratory flow between 25 and 75 percent of FVC (FEF25-75), forced expiratory volume in one second, peak expiratory flow (PEF) and diffusion capacity. Additionally, oxygen saturation as assessed by pulse oximetry is required. Perform at baseline and subsequently at the discretion of the investigator. Hemoglobin must be obtained within 3 days of pulmonary function testing.

23 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.

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	Every 12 Weeks (± 7 days) or as directed by the Sponsor
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	± 3 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]	←	—	—	—	→
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 and Weight [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 Chemistry Panel [8]	X				
T3/**FT3**, FT4 and TSH [9]	X				
Patient Reported Outcomes					
EuroQoL EQ-5D [10]	X				
EORTC QLQ-C30 [10]	X				
EORTC QLQ LC-13 [10]	X				
Health Economic Assessment [10]	X				

1 The mandatory Safety Follow-Up Visit should be conducted approximately 30 days after the last dose of trial treatment regardless of initiation of new antineoplastic treatment. Subjects who are eligible per the requirements in Section 7.1.5.4 for treatment with MK-3475 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.

2 Subjects who discontinue trial treatment for a reason other than disease progression will move into the Follow-up Phase and should be assessed by radiologic imaging to monitor disease status every 9 weeks (63 ± 7 days) through Week 54, and then every 12 weeks (84± 7 days) thereafter. 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) through Week 54 and then every 12 weeks (84 ± 7 days) thereafter 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, death, or entering the Second Course Phase, whichever occurs first.

3 Once a subject experiences disease progression (and does not continue into the Second Course Phase) or starts a new antineoplastic therapy, the subject moves into the Survival Follow-up Phase and should be contacted by telephone approximately every 12 weeks 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 participants who do not/will not have a scheduled study visit or study contact during the Sponsor defined time period will be contacted for their survival status (excluding participants that have withdrawn consent or have a death event previously recorded).

4 Record all AEs occurring within 30 days after the last dose of trial treatment. Report all SAEs (related and unrelated to trial treatment), ECIs, and irAEs occurring within 90 days of the last dose of trial treatment or the start of new anti-cancer treatment, whichever comes first. After this time, report only SAEs and ECIs 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. Unless a subject enters the Second Course Phase, imaging should continue until the start of a new antineoplastic therapy, documented disease progression, or death, whichever occurs first. Subjects who enter the Second Course Phase will be assessed every 12 weeks (84 ± 7 days) by radiologic imaging as described in the Second Course Phase Flow Chart.

7 Subjects who discontinue trial treatment due to reasons other than disease progression should continue to be assessed every 9 weeks (63 ± 7 days) through Week 54 and then every 12 weeks (84 ± 7 days) thereafter by radiologic imaging calculated from the study treatment start day.

8 See Section 7.1.3 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 electronically by subjects in the following order: EuroQol EQ-5D first, then EORTC QLQ C-30, and lastly the EORTC LC-13. It is most relevant and strongly recommended that ePROs are administered prior to study drug administration, adverse event evaluation and disease status notification. HEA will be completed by qualified site personnel after the subject completes all other questionnaires. Once the subjects enter the crossover, ePROs will not be collected for crossover subjects,

6.3 Second Course Phase

6.3.1 Second Course Phase for MK-3475 200 mg Q3W Arms

Trial Phase	Second Course Treatment Cycles[1]														End of Treatment
Treatment Cycle / Scheduled Time	1	2	3	4	5	6	7	8	9	10	11	12	13	14 to 17	Discontinuation Visit
Scheduling Window (Days):[2]		± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	
Administrative Procedures															
Eligibility Criteria[3]	X														
Concomitant Medications[4]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Trial Treatment Administration	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Clinical Procedures / Assessments															
Review Adverse Events [5, 6]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Full Physical Examination	X			X			X			X			X	X[7]	
Directed Physical Examination		X	X		X	X		X	X		X	X		X[7]	X
Vital Signs and Weight [8]	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
Laboratory Procedures / Assessments: analysis performed by local laboratory															
Pregnancy Test - Urine or Serum β-HCG [9]	X														
PT/INR and aPTT [10]	X [11]														
CBC with Differential[12]	X [11]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Comprehensive Chemistry Panel[12]	X [11]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis[12]	X [11]				X				X				X	X[13]	X
T3/**FT3**, FT4 and TSH [12, 14]	X [11]	X		**X**		**X**		**X**		**X**		**X**		**X [13]**	X
Efficacy Measurements															
Tumor Imaging [15, 16]	X			X			X			X			X	X[15]	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); however the treatment cycle interval may be increased due to toxicity according to the dose modification guidelines provided in Section 5.2.1.2. If 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 12 weeks (84 ± 7 days) from the first dose of trial treatment regardless of any treatment delays.

2 In general, the window for each visit is ± 3 days unless otherwise specified.

3 Review Secord Course Phase eligibility criteria in Section 7.1.5.4 prior to administering the first dose of trial treatment.

4 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 ECI as defined in Section 7.2.
5 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.
6 All AEs of unknown etiology associated with trial treatment exposure should be evaluated to determine if it is possibly an ECI. (See the separate guidance document in the administrative binder regarding identification, evaluation and management of AEs of a potential immunologic etiology).
7 Perform a full physical examination every 3 cycles after Cycle 13. Otherwise, perform a directed physical examination the day of the study treatment visit.
8 Vital signs to include temperature, pulse, respiratory rate, weight and blood pressure.
9 For women of reproductive potential, 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.
10 Coagulation factors (PT/INR and aPTT) should be monitored closely throughout the trial for any subject receiving anticoagulant therapy.
11 Laboratory tests for determining eligibility for Second Course Phase are to be performed within 10 days prior to the first dose of MK-3475. See Section 7.1.3 for details regarding laboratory tests.
12 After the first dose, lab samples can be collected up to 48 hours 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.
13 Perform every 4 cycles after Cycle 13; perform thyroid testing every other cycle.
14 Thyroid function tests will be performed by a central laboratory only if the local laboratory is unable to perform this service.
15 The Second Course Cycle 1 scan may have been performed up to 30 days prior to the first dose of trial treatment in the Second Course Phase. Imaging will be performed every 12 weeks (84 ± 7 days) after the first dose of Second Course Phase trial treatment or more frequently if clinically indicated. The timing of imaging should follow calendar days and should not be adjusted for delays in cycle starts or extension of MK-3475 cycle frequencies. The same imaging technique should be used in a subject throughout the trial. Local reading (investigator assessment with site radiology reading) will be used to for subject management; Sponsor will collect radiological assessments for retrospective analysis by a central vendor. The processes for image collection and transmission to the central vendor are in the investigator Imaging Operations Manual (IIOM).
16 After the first documentation of progression (if the subject is clinically stable) or responses per irRC, confirmatory imaging. Confirmatory imaging scan should be performed at the next scheduled time point (i.e., every 63 +/- 7 days).

6.4 Second Course 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 12 weeks (84 days) after Month 6	Every 12 Weeks
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	± 3 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]	←	———	———	———	→
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 and Weight [5]	X	X	X		
Efficacy Measurement					
Tumor Imaging [6]	X [6]	X	X	X	
Laboratory Procedures/Assessments: analysis performed by local laboratory					
CBC with Differential [7]	X				
Comprehensive Chemistry Panel[7]	X				
T3/**FT3**, FT4 and TSH [8]	X				

1 The mandatory Safety Follow-Up Visit should be conducted approximately 30 days after the last dose of trial treatment regardless of initiation of new antineoplastic treatment. Subjects who are eligible per the requirements in Section 7.1.5.4 for treatment with MK-3475 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.

2 Subjects who discontinue trial treatment for a reason other than disease progression will move into the Follow-up Phase and should be assessed by radiologic imaging to monitor disease status every 12 weeks (84 ± 7 days). 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 by radiologic imaging to monitor disease status, development of drug related SAEs and ECIs, and initiation of new antineoplastic therapy every 12 weeks (84 ± 7 days). 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 every 12 weeks 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 participants who do not/will not have a scheduled study visit or study contact during the Sponsor defined time period will be contacted for their survival status (excluding participants that have withdrawn consent or have a death event previously recorded).

4 Record all AEs occurring within 30 days after the last dose of trial treatment.. Report all SAEs (related and unrelated to trial treatment), ECIs, and irAEs occurring within 90 days of the last dose of trial treatment or the start of new anti-cancer treatment, whichever comes first. After this time, report only SAEs and ECIs 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. Subjects, who discontinue trial treatment due to reasons other than disease progression, should continue to be assessed by radiologic imaging every 12 weeks (84 ± 7 days), calculated from the first date of study treatment, until the start of a new antineoplastic therapy, documented disease progression, or death, whichever occurs first.
7 See Section 7.1.3 for list of laboratory tests.
8 Analysis will be performed by a central laboratory only if the local laboratory is unable to perform this service.

6.5 Crossover Phase

Subjects who were randomized to docetaxel and had experienced disease progression while receiving docetaxel in the study or who, after participating in the study, started subsequent anti-cancer therapy and then experienced progression are eligible for the Crossover Phase.

Subjects who discontinue study treatment of the Crossover Phase will follow the same Post-Treatment Follow-up Phase Flow Chart.

	Treatment Cycles[1]														End of Treatment	Survival Follow-up
Treatment Cycle / Scheduled Time	1[7]	2	3	4	5	6	7	8	9	10	11	12	13	14 through 35	Discontinuation Visit	Every 12 Weeks
Scheduling Window (Days):[2]		± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3		
Administrative Procedures																
Informed Consent	X															
Inclusion/Exclusion Criteria	X															
Previous Anti-Cancer Therapy[10]															X	
Prior and Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Clinical Procedures / Assessments																
Review Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Full Physical Examination	X			X			X			X			X	X[12]	X	
Directed Physical Examination		X	X	X	X	X	X	X	X	X	X	X	X	X		
Vital Signs and Weight	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	
Laboratory Procedures / Assessments: analysis performed by local laboratory																
CBC with Differential[9]	X[3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
PT/INR and aPTT	X[3]															
Comprehensive Serum Chemistry Panel	X[3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Urinalysis	X[3]				X				X				X	X[11]	X	

	Treatment Cycles[1]														End of Treatment	Survival Follow-up
Treatment Cycle / Scheduled Time	1[7]	2	3	4	5	6	7	8	9	10	11	12	13	14 through 35	Discontinuation Visit	Every 12 Weeks
Scheduling Window (Days):[2]		± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3		
T3/FT3, FT4 and TSH [4, 5]	X[3]	X		X		X		X		X		X		X[4]	X	
Efficacy Measurements																
Survival Status	←													→		X[13]
Tumor Imaging [6]	X				X				X			X		X[6]	X	
Study Drug Administration																
MK-3475[8]	X	X	X	X	X	X	X	X	X	X	X	X	X	X		

1 In general, assessments/procedures are to be performed on Day 1 of crossover study and prior to the first dose of study medication and for each dose of following cycle unless otherwise specified. Progressive disease from docetaxel or subsequent anti-cancer therapies based on investigator's assessment (either radiographic or clinical) is required. Treatment cycles are 3 weeks (21-days). Imaging will be performed every 9 weeks (63 ± 7 days) from the first dose of trial treatment regardless of any treatment delays through Week 54, and then every 12 weeks (84 ± 7 days) thereafter.

2 In general, the window for each visit is ± 3 days unless otherwise specified.

3 Laboratory tests are to be performed within 10 days prior to the first dose of trial treatment. See Section 7.1.3 for details regarding laboratory tests.

4 Perform thyroid testing every other cycle.

5 Thyroid function tests will be performed by a central laboratory only if the local laboratory is unable to perform this service.

6 Baseline imaging for the crossover phase should be done within 30 days of the first dose of crossover study medication. On study imaging will be performed every 9 weeks (63 ± 7 days) after the first dose of trial treatment through Week 54, and then every 12 weeks (84 ± 7 days) thereafter, or more frequently if clinically indicated. The timing for imaging studies should follow calendar days and should not be adjusted for delays in cycle starts or extension of MK-3475 cycle frequencies. The same imaging technique should be used in a subject throughout the trial. Local reading (investigator assessment with site radiology reading) will be used to determine eligibility and for subject management. Images done in the study including baseline scan should be submitted to a central imaging vendor. The processes for image collection and transmission to the central vendor are in the investigator Imaging Operations Manual (IIOM).

7 Screening can initiate when investigator decides subjects meet inclusion and exclusion criteria for the crossover phase. Wash out period from last dose of docetaxel or anti-cancer therapy is left to investigator discretion while ensuring that patient will have adequate time to recover from any AEs of the previous anti-cancer therapies.

8 Wash out period from last dose of docetaxel or anti-cancer therapy is left to investigator discretion while ensuring that patient will have adequate time to recover from any AEs of the previous anti-cancer therapies. Subjects will continue in trial until progressive disease is confirmed as assessed by irRC as determined by the investigators or up to two years from initiation of a new anti-cancer therapy, whichever comes first.

9 After cycle 1, lab samples can be collected up to 48 hours prior to the scheduled time point.

10 If patient is entering the Crossover Phase after experiencing an anti-cancer therapy, the previous anti-cancer therapy must be recorded in the EDC system.

11 Perform every 4 cycles after cycle 13.

12 Perform every 3 cycles after cycle 13.

13. 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 12 weeks 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 participants who do not/will not have a scheduled study visit or study contact during the Sponsor defined time period will be contacted for their survival status (excluding participants that have a death event previously recorded)

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 must obtain documented consent from each potential subject 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 after the subject provides written informed consent.

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 starting the trial. In addition, record all treatments for a prior cancer other than NSCLC even if taken greater than 30 days prior to Visit 1. 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 still occur approximately 30 days after last dose of study therapy. Once new antineoplastic therapy has been initiated the subject will move into survival follow-up after the 30 day safety visit.

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 Randomization Number

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

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

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

Interruptions from the protocol specified treatment plan for greater than 12 weeks between MK-3475 doses due to toxicity 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 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. Following the guidance described in Section 7.2.3.2., certain irAEs should also be reported to the Sponsor as ECIs.

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. Clinically significant abnormal findings should be recorded as medical history. The timepoints for full physical exam are described in Section 6 - Trial Flow Chart. 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.

7.1.2.3 Vital Signs

The investigator or qualified designee will take vital signs 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. 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. Additional timepoints for standard 12-lead ECG are described in Section 6 – Trial Flow Chart.

An analysis of subjects receiving MK-3475 from protocol number 001 which correlates their QTc interval with PK parameters will occur several months after the initiation of PN010 to demonstrate that the upper bound of the confidence interval for median change in QTc from baseline to maximum steady state plasma concentration of MK-3475 is not above 20 milliseconds. When data from this analysis demonstrates that MK-3475 has a low likelihood of increasing the QTc interval, the collection of ECG data in this study during treatment will discontinue. Sites will be notified via Administrative Memo of this change. Enough on treatment ECG data has been collected such that further collection is not required. A significant prolongation of the QTc interval by MK-3475 has not been observed.

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 Pulmonary Function Tests

Pulmonary function tests should include an assessment of forced vital capacity, forced expiratory flow between 25 and 75 percent of FVC (FEF25-75), forced expiratory volume in one second and peak expiratory flow (PEF) and diffusion capacity. Additionally, oxygen saturation as assessed by pulse oximetry is required. These tests should be performed at baseline and subsequently at the discretion of the investigator. Hemoglobin must be obtained within 3 days of pulmonary function testing.

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, Urinalysis and Other)

Laboratory tests are specified in Table 5.

Table 5 Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Blood	PT (INR)
Hemoglobin	Alkaline phosphatase	Glucose	aPTT
Platelet count	Alanine aminotransferase (ALT)	Protein	Triiodothyronine (T3) or Free Triiodothyronine
WBC (total and differential)	Aspartate aminotransferase (AST)	Specific gravity	Free thyroxine (FT4)
Red Blood Cell Count	Lactate dehydrogenase (LDH)	Microscopic exam, if abnormal results are noted	Thyroid stimulating hormone (TSH)
Absolute Neutrophil Count	Carbon Dioxide (CO_2 or bicarbonate)***	Urine pregnancy test*	Serum β-human chorionic gonadotropin (β-hCG)*
Absolute Lymphocyte Count	Creatinine or calculated creatinine clearance (CrCl)		Anti-MK-3475 Antibodies
	Uric acid		PK
	Calcium		Blood for FBR
	Chloride		GFR
	Glucose		
	Phosphorus		
	Potassium		
	Sodium		
	Magnesium		
	Total Bilirubin		
	Direct and indirect Bilirubin		
	Total protein		
	Blood Urea Nitrogen		
	Total Cholesterol		
	Triglycerides		

* Perform on women of child bearing potential only. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required.
** White Blood Cell Differential (Absolute) is required. White Blood Cell Differential (%) is required only if customarily reported in your region. If White Blood Cell Differential (%) is not normally done then these fields can be left blank and no comment is required.
*** If this test is not done as part of local standard of care, this test does not need to be performed.

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 48 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 Pharmacokinetic Evaluations

7.1.3.2.1 Blood Collection for Serum MK-3475

Sample collection, storage and shipment instructions for serum samples will be provided in the operations/laboratory manual.

The timepoints for PK blood sampling are described in Section 6 - Trial Flow Chart.

In protocol amendment 13 and beyond, PK and ADA samples will not be collected.

7.1.3.3 Anti-MK-3475 Antibodies

Sample collection, storage and shipment instructions will be provided in the operations/laboratory manual.

In protocol amendment 13 and beyond, PK and ADA samples will not be collected.

7.1.3.4 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.

7.1.3.5 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 Tumor Imaging

The site's study team must have reviewed pre-trial images from at least 2 dates to confirm that radiographic progression has occurred per RECIST 1.1 following initiation of the first-line platinum-containing doublet. The central imaging vendor must have received these scans prior to randomization in this trial for a possible retrospective analysis of this eligibility criterion. The central imaging vendor must also confirm that pre-trial scans are of diagnostic quality prior to randomization.

The initial tumor imaging will be performed within 30 days prior to the first dose of trial treatment. Scans performed as part of routine clinical management are acceptable for use as the screening scan if they are of diagnostic quality and performed within 30 days prior to the first dose of trial treatment. On-study imaging will be performed every 9 weeks (63 ±

7 days) after the first dose of trial treatment, and every 12 weeks (84 ± 7 days) from Week 54 onward. Imaging may be performed more frequently if clinically indicated. CT timing should follow calendar days and should not be adjusted for delays in cycle starts or extension of MK-3475 cycle frequencies.

After the first documentation of progression (if the subject is clinically stable), or response per irRC, confirmatory scans will be performed as at the next scheduled time point (e.g. every 63 ±7 days).

After the first documentation of progression it is at the discretion of the investigator to keep a clinically stable subject on trial treatment or to stop trial treatment until repeat imaging performed at the next scheduled time point (i.e., every 63 +/- 7 days) confirms progression. Clinical Stability is defined as:

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

2. No decline in ECOG performance status.

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

Subjects that are deemed clinically unstable are not required to have repeat imaging for confirmation. If progression is confirmed, then the subject will be discontinued from trial treatment. If progression is not confirmed, then the subject should resume/continue trial treatment and have their next scan according to their current imaging schedule (every 9 weeks [63 ± 7 days] from first dose of study treatment through Week 54, and every 12 weeks [84 ± 7 days] thereafter). When feasible, subjects should not be discontinued until progression is confirmed.

Imaging during the follow-up period is to be repeated every 9 weeks (63 ± 7 days) from C1D1 through Week 54, and every 12 weeks (84 days ± 7 days) thereafter, for subjects who discontinue trial treatment for reasons other than disease progression until the subject experiences confirmed disease progression or starts a new antineoplastic therapy. Subjects who move into the Second Course Phase will continue to have scans performed every 12 weeks (84 days ± 7 days) relative to C1D1 of Second Course Phase until the subject experiences confirmed disease progression or starts a new antineoplastic therapy.

Disease progression for trial eligibility will be according to RECIST 1.1 criteria; however disease response on trial will be assessed using irRC (see Section 12.6) by investigators. A central group of independent radiologists will review all on-study images to make response assessments per RECIST 1.1 (see Section 12.7). Local reading (investigator assessment with site radiology reading) will be used to determine eligibility and for subject management; Sponsor will collect radiological assessments per inclusion criteria 5 for a potential retrospective analysis of subject eligibility by a central vendor.

The same imaging technique should be used in a subject throughout the trial. The processes for image collection, processing and transmission to the central vendor are in the investigator Imaging Operations Manual (IIOM).

7.1.4.2 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 electronically by subjects prior to all other study procedures in the following order: EuroQol EQ-5D first, then EORTC QLQ C-30, and lastly the EORTC LC-13 at the time points specified in the Trial Flow Chart. It is most relevant and strongly recommended that ePROs are administered prior to study drug administration, adverse event evaluation and disease status notification.

In protocol amendment 13 and beyond, ePROs will not be collected for crossover subjects.

The health economic assessment (HEA) form will be completed by qualified site personnel after the subject completes all other questionnaires. The form captures non-study related healthcare visits, including healthcare provider visits, emergency room (ER) visits, and hospitalizations (including admission and discharge dates and primary discharge diagnosis).

7.1.4.3 Tumor Tissue Collection

Tumor tissue for biomarker analysis from a newly obtained formalin fixed biopsy of a tumor lesion not previously irradiated must be received by the central vendor before randomization for determination of PD-L1 expression; no systemic antineoplastic therapy may be administered between the PD-L1 biopsy and initiating study medication. Only subjects whose tumors demonstrate evidence of PD-L1 expression (on the neoplastic cells) are eligible for enrollment. Patients will be stratified between strongly positive and weakly positive PD-L1 expression before randomization. A fine needle aspirate or cytologic specimen will not be acceptable. Needle or excisional biopsies, or resected tissue is required. Newly obtained formalin fixed specimens are required.

Archival material may be used for determination of EGFR and ALK status. 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 MK-3475. Patients who agree to undergo these additional, optional tumor biopsies while receiving MK-3475 may not have them under CT guidance.

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.

7.1.4.4 Withdrawal/Discontinuation

When a subject discontinues/withdraws prior to trial completion, 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.

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

In the event that the medical records for the main trial are no longer available (e.g., if the investigator is no longer required by regulatory 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.

7.1.4.5 Blinding/Unblinding

Study treatment is open label in this study.

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 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.
- Tumor imaging must be performed within 30 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 up at scheduled visits until the start of new antineoplastic therapy, disease progression, pregnancy, death, withdrawal of consent, or is lost to follow-up. Except for those who withdraw consent, subjects will enter the survival follow-up phase. If the subject experienced a CR, PR, or SD during the treatment Phase on MK-3475, and then experiences PD at any time during that follow-up period, he/she will be eligible to receive up to 17 cycles (approximately 1 year) of therapy with MK-3475 in the Second Course Phase. After the Second Course Phase subjects should be followed up until the start of new antineoplastic therapy, disease progression, death, or is lost to follow-up., with no option for retreatment with MK-3475 on study.

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. 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 MK-3475 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 by radiologic imaging to monitor disease status and initiation of new antineoplastic therapy every 9 weeks (63 ± 7 days) through Week 54, and every 12 weeks (84 ± 7 days) thereafter. Unless otherwise noted in the flow chart, every effort should be made to collect subject information on the start of new antineoplastic therapy, disease progression, death.

Subjects who are eligible to receive treatment with MK-3475 in the Second Course Phase according to the criteria in Section 7.1.5.4 will move from the follow-up phase to the Second Course Phase when they experience disease progression. Subjects who discontinue trial treatment from the Second Course Phase for a reason other than disease progression will move into the Follow-up Phase and should continue to be assessed every 12 weeks (84 ± 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) through Week 54 and every 12 weeks (84 ± 7 days) thereafter 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, disease progression, and 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 (63 ± 7 days) through Week 54 and every 12 weeks (84 ± 7 days) thereafter until PD is identified. Once the subject stops the imaging assessments for this protocol (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 every 12 weeks to assess for survival status. Post-study treatments and the subject's response to them will also be collected.

7.1.5.3.4 Survival Status

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

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 MK-3475 may be eligible to receive MK-3475 200 mg IV Q3W in the Second Course Phase of this study for up to 17 cycles (approximately 1 year) if the subject:

- Stopped their initial treatment with MK-3475 after attaining an investigator-determined confirmed CR according to irRC, was treated for at least six months with MK-3475, and received at least two treatments with MK-3475 beyond the date when the initial CR was declared. A CR by irRC means that all index lesions have resolved (none have bidimensional measurements), all non-index lesions have disappeared, and no new lesions have been identified. These findings must be confirmed on subsequent imaging performed at the next scheduled time point (i.e., every 63 +/- 7 days) for the call of CR by irRC to be appropriate. So the patient will have no evidence of metastatic cancer in order for the subject and his/her physician to consider the subject's participation in this Second Course Phase.
- Experienced an investigator-determined confirmed radiographic disease progression according to irRC after stopping their initial treatment with MK-3475 due to achievement of a confirmed CR or have experienced 35 administrations of MK-3475.
- Did not receive any anti-cancer treatment since the last dose of MK-3475.
- Have a life expectancy of at least 3 months.
- Have a performance status of 0 or 1 on the ECOG Performance Scale.
- Have adequate organ function as indicated in Table 1.
- Female subject of childbearing potential has a negative urine or serum pregnancy test. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. The serum pregnancy test must be negative for the subject to be eligible.
- Be willing to adhere to the contraception requirements (see Section 5.7.2)

- Does not meet the following exclusion criteria:
    - Is receiving systemic steroid therapy ≤7 days prior to the first dose of trial treatment or receiving any other form of immunosuppressive medication.

        a) Corticosteroid use on study after Cycle 1 for management of AEs, SAEs, and events of clinical interest (ECIs), as a pre-medication for IV contrast allergies/reactions or if considered necessary for a subject's welfare, is allowed.

        b) Subjects who receive daily steroid replacement therapy serve as an exception to this rule. Daily prednisone at doses of 5 to 7.5 mg (or hydrocortisone equivalent doses) is an example of replacement therapy.

        c) Subjects who use inhaled steroids for the control of asthma serve as an exception to this rule.

    - 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).

    - Has an active autoimmune disease, or a documented history of autoimmune disease, or a syndrome that requires systemic steroids or immunosuppressive agents. Subjects with vitiligo or resolved childhood asthma/atopy would be exception to this rule. Subjects that require inhaled steroid or local steroid injections will not be excluded from the study. Subjects with hypothyroidism not from autoimmune disease and stable on hormone replacement will not be excluded from the study.

    - Has had an allogeneic tissue/solid organ transplant.

    - Has interstitial lung disease or a history of pneumonitis that required oral or intravenous glucocorticoids to assist with management. Lymphangitic spread of the NSCLC is not exclusionary.

    - 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.

    - Has an active infection requiring intravenous systemic therapy.

    - Has known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).

- 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.

- 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.

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

- 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).

- Subjects will be re-treated at MK-3475 200 mg Q3W. An objective response or progression of disease that occurs during the Second Course Phase for a patient will not be counted as an event for the primary analysis of either endpoint in this trial.

7.1.5.5 Crossover for Subjects in the Docetaxel Arm to MK-3475 200 mg Arm

Subjects who were randomized to the docetaxel arm and had experienced disease progression (either clinically or radiographically) while receiving docetaxel in PN010 or from subsequent anti-cancer therapy, are eligible for the crossover phase to receive MK-3475 200 mg Q3W. Subjects who permanently discontinued from the study by withdrawal of consent are not eligible for crossover.

There are no laboratory requirements or limitations to enter the Crossover Phase. Subjects will have laboratory assessments while receiving study treatment as outlined in the Crossover Flow Chart in Section 6.5.

7.1.5.5.1 Inclusion Criteria for Optional Crossover from docetaxel to MK-3475 200 mg arm

In order to be eligible for participation in the crossover phase, the subject must:

- Be willing and able to provide written informed consent/assent for the trial.

- Have been randomized into the docetaxel arm of MK-3475 PN010 study and taken at least one dose of study medication

- Have experienced disease progression (either clinical or radiographic, as assessed by the investigator) from docetaxel or other subsequent anti-cancer therapies.

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

- Subjects with known and treated brain metastasis are eligible provided they are clinically stable, and brain metastases have been treated. Steroid use for symptom control is allowed but the total daily dose should be ≤ 10 mg of prednisone or its equivalent.

- Have baseline imaging scan done within 30 days of the first dose of MK-3475

- Have adequately recovered from adverse events of previous anti-cancer therapy.

- Be willing to adhere to the contraception requirements (see Section 5.7.2).

7.1.5.5.2 Exclusion Criteria for Optional Crossover from docetaxel to MK-3475 200 mg arm

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

- Has withdrawn consent from study (MK-3475 PN010).

- Have active pneumonitis of Grade 2 or greater or history of pneumonitis requiring systemic steroid therapy.

- Has received thoracic radiation therapy of > 30 Gy within 6 months have active and untreated brain metastasis

7.1.5.6 Crossover Assessments and Procedures

Crossover subjects can initiate treatment with MK-3475 200 mg Q3W after their last dose of docetaxel or after their last dose of chemotherapy once investigators confirm that subjects are meeting inclusion and exclusion criteria for the Crossover Phase as listed in Section 7.1.5.5. The subject will then start the Crossover Phase as outlined in Crossover Flow Chart in Section 6.5. Subjects must have baseline imaging scans performed within 30 days prior to the first dose in the Crossover Phase. On study, imaging will be performed every 9 weeks (63 ± 7 days) after the first dose of crossover trial treatment through Week 54, and every 12 weeks (84 ± 7 days) thereafter, or more frequently, if clinically indicated. Local reading (investigator assessment with site radiology reading) will be used to determine eligibility and for subject management. All scans performed during the study should be submitted to the imaging vendor for independent, central reading.

Subjects who attain irCR per irRC will have an option to hold MK-3475 while continuing in the trial. Subjects will continue in trial until progressive disease is confirmed as assessed by irRC as determined by the investigators or up to two years from starting crossover therapy with MK-3475 200 mg Q3W, whichever comes first. Subjects who discontinue study medication in the Crossover Phase will follow the post treatment phase procedures as outlined in Section 6.2. Crossover subjects will not be eligible for second course phase as outlined in Section 6.3.

7.1.6 Post Final Analysis Activities

If at IA2 or the final analysis the DMC recommends a crossover of patients from docetaxel to MK-3475 treatment based on OS data, all patients with a randomization number in this study, if they still meet certain inclusion criteria, may be offered further therapy with MK-3475; the details of which will be discussed in a future communication.

7.2 Assessing and Recording Adverse Events

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

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

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

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

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

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

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

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

In this trial, an overdose is any dose higher than 20% over the prescribed dose.

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

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

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

7.2.2 Reporting of Pregnancy and Lactation to the Sponsor

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

Pregnancies and lactations that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure. Pregnancies and lactations that occur from the time of treatment allocation/randomization through 120 days following cessation of Sponsor's product (or 180 days for subjects assigned to docetaxel), or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, must be reported by the investigator. All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

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

7.2.3 Immediate Reporting of Adverse Events and Incidents 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 6 for additional details regarding each of the above criteria.

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

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

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

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

7.2.3.2 Events of Clinical Interest

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

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

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

Events of clinical interest for this trial include:

A. 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.

B. 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.

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

ECIs that occur to any subject from the date of first dose through 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, whether or not related to the Sponsor's product, must

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

7.2.3.3 Protocol-Specific Exceptions to Serious 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, unless there is evidence suggesting a causal relationship between the drug and the event. Any such event will be submitted to the Sponsor within 24 hours either by electronic or paper media.

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.

7.2.3.4 Device Events

For this protocol, an Adverse Device Event (ADE) is any adverse health outcome related to the use of the in vitro diagnostic product (IVD). ADEs include any malfunction or deterioration in the characteristics and/or performance of the IVD, as well as any inadequacy in the labeling or the instructions for use, that directly or indirectly, led to, or could have led to a death or serious deterioration of the patient's health.

A serious deterioration in the state of health can include:

1. Life-threatening illness or injury;

2. Permanent impairment of a body function or permanent damage to a body structure;

3. A condition necessitating medical or surgical intervention to prevent 1 or 2;

4. A condition that requires hospitalization or significant prolongation of existing hospitalization; or

5. Fetal distress, fetal death or any congenital abnormalities or birth defects.

In addition, any false positive or false negative test results, whether or not they impact the patient's health, must be reported.

Any such event, including follow up to an event, that occurs to any patient from the time the consent is signed through the end of the study, must be reported within 24 hours to the Sponsor either by electronic media or paper. Sponsor Contact information can be found in the Investigator Trial File Binder.

Additionally, any such event considered by an investigator who is a qualified physician to be related to the IVD that is brought to the attention of the investigator at any time after the study also must be reported immediately to the Sponsor.

All such events must be followed up for outcome.

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 6 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 [including hospitalization for an elective procedure] for a preexisting condition which has not worsened does not constitute a serious adverse event.); 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 U.S. CLINICAL MONITOR AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL.
	Consistency with Trial Treatment Profile	Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Sponsor's product or drug class pharmacology or toxicology?
The assessment of relationship will be reported on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.		
Record one of the following	**Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Sponsor's product relationship).**	
Yes, there is a reasonable possibility of Sponsor's product relationship.	There is evidence of exposure to the Sponsor's product. The temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable. The AE is more likely explained by the Sponsor's product than by another cause.	
No, there is not a reasonable possibility of Sponsor's product relationship	Subject did not receive the Sponsor's product OR temporal sequence of the AE onset relative to administration of the Sponsor's product is not reasonable OR the AE is more likely explained by another cause than the Sponsor's product. (Also entered for a subject with overdose without an associated AE.)	

7.2.5 Sponsor Responsibility for Reporting Adverse Events

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

7.3 TRIAL GOVERNANCE AND OVERSIGHT

7.3.1 Scientific Advisory Committee

This trial was developed in collaboration with a Scientific Advisory Committee (SAC). The SAC comprises both Sponsor and non-Sponsor scientific experts who provide input with respect to trial design, interpretation of trial results and subsequent peer-reviewed scientific publications.

7.3.2 Trial Steering Committee

This trial will be conducted in consultation with a Trial Steering Committee. The Trial Steering Committee comprises:

- Sponsor personnel
- Investigators participating in the trial
- Consulting therapeutic-area experts and clinical trialists

The Trial Steering Committee will provide guidance on the operational aspects of the trial, evaluate recommendations from the Data Monitoring Committee (DMC) and make recommendations to the Executive Oversight Committee (EOC).

Specific details regarding responsibilities and governance of the Trial Steering Committee will be described in a separate charter.

7.3.3 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 (DMC) regarding the trial.

7.3.4 Data Monitoring Committee

To supplement the routine trial monitoring outlined in this protocol, an external Data Monitoring Committee (DMC) will monitor the interim data from this trial. The voting members of the committee are external to the Sponsor. The members of the DMC 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 DMC will include 3 clinicians experienced in Lung Cancer and 1 external statistician; this is in addition to the unblinded trial statistician who will be a non-voting member of the committee.

The DMC will make recommendations to the EOC regarding steps to ensure both subject safety and the continued ethical integrity of the trial. Also, the DMC will review interim trial results, consider the overall risk and benefit to trial participants (see Section 8.1.5 and 8.2.9 - Interim Analyses) 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 DMC reports, minutes, and recommendations will be described in a separate charter that is reviewed and approved by the DMC. The DMC will monitor the trial at an appropriate frequency, as described in the detailed DMC charter. The DMC will also make recommendations to the Sponsor protocol team regarding steps to ensure both subject safety and the continued ethical integrity of the trial.

A DMC recommendation will be communicated to the Sponsor as agreed to in the Collaboration agreement.

8.0 STATISTICAL ANALYSIS PLAN

8.1 Statistical Analysis Plan Summary

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

8.1.1 Efficacy Analyses

The intention-to-treat (ITT) population in the strongly positive PD-L1 stratum and the overall positive PD-L1 population will serve as the primary population for the analyses of efficacy data in this trial. The primary efficacy endpoints are overall survival (OS) (i.e., the time from randomization to death due to any cause) and progression-free survival (PFS) (i.e., time from randomization to documented progressive disease or death due to any cause, whichever occurs first) per RECIST 1.1 based on blinded independent radiologists' review. Type I error is strongly controlled at 2.5% (one-sided) for tests of PFS and OS in both the strongly positive PD-L1 stratum and the overall PD-L1 positive population. The secondary objectives for this trial are overall response rate (ORR) and response duration per RECIST 1.1 based on blinded independent radiologists' review. The same endpoints will be applied to analyses of the overall population. In addition, PFS, ORR and response duration per irRC based on investigators' reviews will also be provided for both populations. An outline of the analysis strategy for key efficacy endpoints is presented in Table 7 below.

Table 7 Primary Analysis Strategy for Key Efficacy Endpoints in Strongly Positive PD-L1 Stratum

Endpoint/Variable (Description, Time Point)	Statistical Method	Analysis Population	Missing Data Approach
Primary:			
Overall survival	Stratified Log-rank test Cox model with Efron's tie handling method for estimation	ITT	Model based
Progression-free survival (RECIST 1.1)	Stratified Log-rank test Cox model with Efron's tie handling method for estimation	ITT	Model based
Secondary:			
Overall response rate (RECIST 1.1)	Stratified Miettinen and Nurminen method	ITT	Subjects with missing data are considered non-responders
Response duration (RECIST 1.1)	Summary statistics using Kaplan-Meier method	All responders in ITT	Non-responders are excluded in analysis

8.1.2 Safety Analyses

The All Patients as Treated (APaT) population in the strongly positive PD-L1 stratum and the overall positive PD-L1 population will be used for the primary analysis of safety data in this study.

Investigators will be asked to report adverse experiences at every visit on this study (at least every 3 weeks during treatment) using Common Terminology Criteria for Adverse Events, Version 4.0. The attribution to drug, time-of-onset, duration of the event, its resolution, and any concomitant medications administered will be reported. AEs will be analyzed and reported for between arm differences in various parameters, including but not limited to all AEs, SAEs, fatal AEs, and laboratory changes. The AE analyses proposed below are supplemental analyses to improve understanding of the relative AEs between MK-3475 and docetaxel and account for the differences in treatment duration between treatment arms.

To properly account for potential difference in follow-up time between the study arms, which is expected to be longer in the MK-3475 arm, the same time-to-event analysis methods as for OS will be used for Tier 1 AE and Grade 3-5 AE based on the time to first event (i.e., the stratified log-rank test will be used for testing the time to AEs, and the stratified Cox model with Efron's tie handling method will be used for estimating the hazard ratio and its 95% confidence interval). Exploratory analysis of the same nature for other AEs that are suspected to have differential follow-up time may also be carried out.

In addition, the p-value and 95% confidence interval for between-treatment difference in the percentage of patients with Grade 3-5 AE overall as well as per cycle for the first four cycles, and the between-treatment difference in the Grade 3-5 AE incidence density adjusted for treatment exposure (duration is defined as from first dose of study drug to 30 days after last

dose of study drug) will be calculated using the stratified Miettinen and Nurminen method [30].

Further, pre-specified adverse events of clinical interest include the following events that are determined to be immune-related by the investigator: 1) Grade ≥ 3 diarrhea 2) Grade ≥ 2 colitis, 3) Grade ≥ 2 pneumonitis, 4) Grade ≥ 3 hypo- or hyperthyroidism. P-values and 95% confidence intervals will be provided for between-treatment differences in the percentage of patients with these events.

8.1.3 Power and Sample Size

The study will randomize subjects in a 1:1:1 ratio into two MK-3475 arms and one docetaxel arm. The sample size for subjects with strongly positive PD-L1 is targeted at approximately 460, and the overall sample size for this study is projected to be approximately 920.

The study is event driven (i.e., number of subjects and follow-up time are subject to change but number of events is not) and will complete after approximately 200 deaths have been observed across three arms in the strongly positive PD-L1 stratum (approximately 140 deaths between one MK-3475 arm and the docetaxel arm under the alternative hypothesis). With 140 deaths between one MK-3475 arm and control, the study has over 81% power to detect a 0.55 hazard ratio at the final analysis, where 0.825% alpha is allocated to the two MK-3475 vs. docetaxel comparisons using Hochberg procedure. The assumptions for the sample size and power calculations are specified in Section 8.2.7.

8.1.4 Multiplicity Adjustment

The multiplicity strategy specified in this section will be applied to the strongly positive PD-L1 stratum and the overall positive PD-L1 population for the testing of primary hypotheses. The Hochberg step-up procedure will be used for multiple comparisons on an efficacy endpoint if both MK-3475 arms continue to study completion. The type I error rates are all one-sided.

The overall type I error is strongly controlled at 2.5% (one-sided) with 0.35% allocated to PFS and 2.15% allocated to OS hypothesis. PFS will be tested in the strongly positive PD-L1 stratum at 0.25% at the second interim analysis (primary analysis of PFS) and at 0.1% at the final analysis for long-term PFS effect. At each analysis, if both MK-3475 arms demonstrate superior PFS in the strongly positive PD-L1 stratum, the corresponding alpha will be rolled into OS testing at the final analysis.

OS will be tested in the strongly positive PD-L1 stratum at 0.5% at the second interim analysis, and at ≥0.825% at the final analysis. At the second interim analysis, only if both MK-3475 arms demonstrate superior OS in the strongly positive PD-L1 stratum, will OS in the overall positive PD-L1 population be sequentially tested at the same alpha level. At the final analysis, OS in the strongly positive PD-L1 stratum and the overall positive PD-L1 population will be tested simultaneously, with available alpha split evenly between the two tests (see Section 8.2.6 for details).

Since the above alpha allocation strategy does not depend on number of events, it remains valid in case actual number of events at an interim analysis or final analysis differs from planned number of events. Based on emerging external data, this testing strategy on PD-L1 may be modified to improve the efficiency of the design before unblinding the biomarker data. Should it happen, a protocol amendment will be issued to document the change which is not expected to impact the conduct of the trial.

8.1.5 Interim Analyses

There are two planned interim analyses in this trial.

Table 8 summaries the strategy and timing of each interim analysis. Accrual will continue during Interim Analyses. The details of interim analyses are provided in the DMC Charter.

Table 8 Summary of Interim Analysis Strategy

Interim Analysis Number	Key Endpoints for Interim Analysis	Anticipated Approximate Timing of Analysis (from study start)	Sample size expected at time of analysis (Three arms)	Primary Purpose of Analysis
Interim Analysis 1	• ORR	App. 10 months	• 120 in strongly positive PD-L1 stratum with 3 months of minimum follow-up	Discontinue one MK-3475 arm for lack of efficacy OR discontinue both arms for futility
Interim Analysis 2 (primary PFS analysis and interim OS analysis)	• PFS/OS	App. 19 months	• App. 414 (around 175 PFS events across three arms) in strongly positive PD-L1 stratum	• Demonstrate superiority of MK-3475 in PFS • Demonstrate superiority of MK-3475 in OS after approximately 120 deaths have been observed across three arms in strongly positive PD-L1 stratum
Final Analysis	OS/PFS	App. 30 months	• App. 460 (around 200 OS events across three arms) in strongly positive PD-L1 stratum	• Demonstrate superiority of MK-3475 in OS • Demonstrate long-term PFS effect of MK-3475

8.2 Statistical Analysis Plan

8.2.1 Responsibility for Analyses/In-House Blinding

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

Although the trial is open label, analyses or summaries generated by randomized treatment assignment, actual treatment received will be limited to clinical safety monitoring and documented. The study team at the Sponsor consisting of clinical, statistical, statistical programming and data management personnel, will be blinded to subject-level PD-L1 biomarker results. An unblinded Sponsor clinical scientist will have access to the subject-level PD-L1 results for the purpose of data review and will have no other responsibilities associated with the study. A summary of PD-L1 biomarker prevalence may be provided to the study team at the Sponsor by the IVRS vendor or an external unblinded statistician.

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

Planned interim analyses are described in Section 8.2.9. Study enrollment will be ongoing at the time of any interim analysis. Access to the allocation schedule for this study will be restricted to an external unblinded statistician and, as needed, a scientific programmer performing the interim analysis, who will have no other responsibilities associated with the study.

Treatment-level results of the interim analysis will be provided by an external unblinded statistician to the eDMC. Key enrollment metrics and study data in the PD-L1 strongly positive stratum will also be monitored by the external unblinded statistician to inform the timing of interim and final analysis. Limited additional SPONSOR personnel may be unblinded to the treatment level results of the interim analyses, if required, in order to act on the recommendations of the eDMC or facilitate regulatory filing after an interim analysis. The extent to which individuals are unblinded with respect to results of interim analyses will be documented by the unblinded statistician.

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 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 committee may be unblinded to results at the treatment level in order to act on these recommendations. Additional logistical details and data monitoring guidance will be provided in the eDMC Charter. Key aspects of the interim analyses are described in Section 8.2.9.

Prior to final study unblinding, the external unblinded statistician will not be involved in any discussions regarding modifications to the protocol, statistical methods, identification of protocol violators, or data validation efforts after the interim analyses.

8.2.2 Hypotheses/Estimation

Objectives and hypotheses of the study are stated in Section 3. The study is considered to have met its primary objective if at least one MK-3475 arm is superior to docetaxel either in PFS or in OS at an interim analysis or the final analysis in subjects with strongly positive PD-L1 expression or overall positive PD-L1 population.

8.2.3 Analysis Endpoints

8.2.3.1 Efficacy/Immunogenicity Endpoints

Primary

There are two primary endpoints of this study: overall survival (OS) and progression-free-survival (PFS) per RECIST 1.1.

Overall Survival

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) per RECIST 1.1

Progression-free survival is defined as the time from randomization to the first documented disease progression per RECIST 1.1 based on blinded independent radiologists' review or death due to any cause, whichever occurs first. See Section 8.2.5.1.3 for definition of censoring.

Secondary

Overall Response Rate (ORR)

Overall response rate is defined as the proportion of the subjects in the analysis population who have a complete response (CR) or partial response (PR). Responses are based on blinded independent radiologists' review per RECIST 1.1. Responses based on investigator's assessments using irRC will also be assessed.

Progression-Free-Survival (PFS) per irRC

Progression-free survival is defined as the time from randomization to the first documented disease progression per irRC based on investigators' review or death due to any cause, whichever occurs first. See Section 8.2.5.1.3 for definition of censoring.

Response Duration

For subjects who demonstrated CR or PR, response duration is defined as the time from first documented evidence of CR or PR until disease progression or death. Response duration for subjects who have not progressed or died at the time of analysis will be censored at the date of their last tumor assessment. Response duration will be calculated for RECIST 1.1 based on blinded independent radiologists' review and for irRC based on investigators' review.

8.2.3.2 Safety Endpoints

Safety measurements are as described in Section 7.

8.2.3.3 Patient Reported Outcomes analysis

EORTC-QLQC30, EORTC QLQ LC-13, EuroQoL EQ-5D, Health Economic Assessment and tumor volumetric changes will be assessed in the exploratory analysis. The EORTC QLQ-C30, EORTC QLQ-LC13, and EQ5D are not pure efficacy or safety endpoints because they are affected by both disease progression and treatment tolerability.

8.2.4 Analysis Populations

8.2.4.1 Efficacy Analysis Populations

The analysis of primary efficacy endpoints are based on the intention-to-treat (ITT) population, i.e., subjects will be included in the treatment group to which they are randomized. A supportive analysis will be conducted in the full analysis set (FAS) that excludes those who did not meet the critical eligibility criteria or discontinued before receiving any dose of assigned treatment.

The primary efficacy analysis will be carried out in the ITT population of the strongly positive PD-L1 stratum and the overall ITT population, including subjects with both strongly and weakly positive PD-L1 expressions.

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

8.2.4.2 Safety Analysis Populations

The All Patients as Treated (APaT) population will be used for the analysis of safety data in this study. The APaT population consists of all randomized subjects who received at least one dose of study treatment. Subjects will be included in the treatment group corresponding to the trial treatment they actually received for the analysis of safety data. Subjects who take incorrect trial treatment for the entire treatment period will be included in the treatment group corresponding to the trial treatment actually received. At least one laboratory or vital sign measurement obtained subsequent to at least one dose of trial treatment is required for inclusion in the analysis of each specific parameter. To assess change from baseline, a baseline measurement is also required.

The primary safety analysis will be based on the APaT population in the strongly positive PD-L1 stratum. In addition, the pooled safety data from both the strongly and weakly positive PD-L1 strata will also be summarized in the secondary safety analysis.

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

8.2.5 Statistical Methods

Statistical testing and inference for safety analyses are described in Section 8.2.5.2. Efficacy results that will be considered to be statistically significant after consideration of the strategy for controlling the Type I error are described in Section 8.2.6, Multiplicity. Nominal p-values may be computed for other efficacy analyses as a measure of strength of association between the endpoint and the treatment effect rather than formal tests of hypotheses.

8.2.5.1 Statistical Methods for Efficacy Analyses

The overall type I error rate for this study is strictly controlled at 2.5% (one-sided) that allows the trial to declare positive in either OS or PFS in the strongly positive PD-L1 stratum. Strong control of Type I error also extends to the analysis of OS in the overall PD-L1 positive population.

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

8.2.5.1.1 Overall Survival (OS)

The Kaplan-Meier method will be used to estimate the survival curves, as well as the overall survival rate at 1 year by treatment group. The treatment difference in survival will be assessed by the stratified log-rank test. A stratified 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 stratified Cox model with a single treatment covariate will be reported. The same stratification factors used for randomization (see Section 5.4) will be applied to both the stratified log-rank test and the stratified Cox model.

Since subjects in the control arm are expected to discontinue treatment earlier compared to subjects in the MK-3475 arm, and subjects discontinued docetaxel treatment may receive other PD-1 treatments similar to MK-3475 after discontinuation, the Rank Preserving Structural Failure Time (RPSFT) model proposed by Robins and Tsiatis [31] will be used to control for receipt of non-study treatment. The RPSFT model provides a randomization-based estimate of treatment effect (RBEE) corrected for the bias induced by crossover. The Kaplan-Meier estimates of the OS rate at 4 months (when most cross-overs are likely to occur), one year and other time points of interest will also be compared between the two treatment groups to explore the confounding effect of subsequent treatments. To further account for the possible confounding effect, a sensitivity analysis of OS that censors subjects

at the time of initiation of new therapy will be performed and an OS analysis that treats initiation of new therapy as a time-dependent binary covariate will also be conducted. In case the proportional hazards assumption doesn't hold, Fleming and Harrington's weighted log-rank test or other methods, as appropriate, will be conducted, after proper adjustment of the crossover effect over time.

Restricted mean survival time (RMST) estimate of OS over time may be calculated as an exploratory analysis.

8.2.5.1.2 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 stratified log-rank test. A stratified 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 stratified Cox model with Efron's method of tie handling and with a single treatment covariate will be reported. The same stratification factors used for randomization (see Section 5.4) will be applied to both the stratified log-rank test and the stratified Cox model.

Since disease progression is assessed periodically, progressive disease (PD) can occur any time 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 first assessment at which PD is objectively documented, regardless of discontinuation of trial treatment. Death is always considered as a confirmed PD event. Subjects without documented PD/death will be censored at the last disease assessment date.

There are three sensitivity analyses with a different set of censoring rules and PD event definitions under various scenarios. The first sensitivity analysis is the same as the primary analysis except that it censors at the last disease assessment without PD when PD or death is documented after more than one missed disease assessment. The second sensitivity analysis is the same as the primary analysis except that it considers discontinuation of treatment or initiation of new anticancer treatment, whichever occurs later, to be a PD event for subjects without documented PD or death. The third sensitivity analysis is the same as the second sensitivity analysis except that it censors at the last disease assessment when there is No PD and no death and new anticancer treatment is initiated. The censoring rules for primary and sensitivity analyses are summarized in Table 9. 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 [32], will 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 9 Censoring Rules for Primary and Sensitivity Analyses of PFS

Situation	Primary Analysis	Sensitivity Analysis 1	Sensitivity Analysis 2	Sensitivity Analysis 3
No PD and no death; new anticancer treatment is not initiated	Censored at last disease assessment	Censored at last disease assessment	Censored at last disease assessment if still on study therapy; progressed at treatment discontinuation otherwise	Censored at last disease assessment
No PD and no death; new anticancer treatment is initiated	Censored at last disease assessment before new anticancer treatment	Censored at last disease assessment before new anticancer treatment	Progressed at date of new anticancer treatment	Censored at last disease assessment
PD or death documented after ≤ 1 missed disease assessment	Progressed at date of documented PD or death	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 after ≥ 2 missed disease assessments	Progressed at date of documented PD or death	Censored at last disease assessment prior to the ≥ 2 missed disease assessment	Progressed at date of documented PD or death	Progressed at date of documented PD or death

In addition to the sensitivity analyses, an exploratory analysis of PFS2, defined as the time from randomization to second/subsequent disease progression after initiation of new anti-cancer therapy, or death from any cause, whichever first, will be carried out. Patients alive and for whom a second objective disease progression has not been observed will be censored at the last time known to be alive and without second objective disease progression. If progression after new anti-cancer therapy cannot be measured, time from randomization until treatment discontinuation, progression or death after new anti-cancer therapy will be measured.

Restricted mean survival time (RMST) estimate of PFS over time may be calculated as an exploratory analysis.

8.2.5.1.3 Overall Response Rate (ORR)

Stratified Miettinen and Nurminen's method [30] will be used for comparison of the overall response rates between the treatment groups. A 95% confidence interval for the difference in response rates between each MK-3475 arm and the control will be provided. A p-value for the difference in response rate between two MK-3475 arms will be provided for dose selection at interim analyses. The same stratification factors used for randomization (see Section 5.4) will be applied to the analysis. A subgroup analysis of ORR will be carried out in patients that have been followed up for 27 weeks, including early drop-outs.

8.2.5.1.4 Response Duration

If sample size permits, response duration will be summarized descriptively using Kaplan-Meier medians and quartiles. Only the subset of subjects who show a complete response or partial response will be included in this analysis.

8.2.5.1.5 Exploratory Analyses

An exploratory analysis of pooled MK-3475 arm vs. docetaxel will be carried out for PFS or OS at the second interim analysis and the final analysis. This pooled analysis will be conducted in the strongly positive PD-L1 stratum as well as the overall PD-L1 positive population. The same stratified Cox proportional hazard model as that for the primary analysis will be used to assess the magnitude of the treatment difference between the pooled MK-3475 arm and docetaxel. The Kaplan-Meier method will be used to estimate the survival curves.

EORTC-QLQC30, EORTC QLQ LC-13, EuroQoL EQ-5D, Health Economic Assessment and tumor volumetric changes will be summarized as part of the exploratory analysis. Details will be provided in a separate document on analysis plan before any unblinding.

The correlation of tumor volumetric changes with OS will be explored by appropriate methods such as the Cox model with the time-dependent covariate of tumor volumetric changes.

8.2.5.2 Statistical Methods for Safety Analyses

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

The analysis of safety results will follow a tiered approach (Table 10). The tiers differ with respect to the analyses that will be performed. Safety parameters or adverse experiences of special interest that are identified *a priori* constitute “Tier 1” safety endpoints that will be subject to inferential testing for statistical significance with p-values and 95% confidence intervals provided for between-group comparisons. Other safety parameters will be considered Tier 2 or Tier 3. 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.

Adverse experiences (specific terms as well as system organ class terms) and predefined limits of change in laboratory, vital signs, and ECG parameters that are not pre-specified as Tier-1 endpoints 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 adverse experiences and predefined limits of change will belong to Tier 3.

The threshold of at least 4 events was chosen because the 95% confidence interval for the between-group difference in percent incidence will always include zero when treatment

groups of equal size each have less than 4 events and thus would add little to the interpretation of potentially meaningful differences. Because many 95% confidence intervals may be provided without adjustment for multiplicity, the confidence intervals should be regarded as a helpful descriptive measure to be used in review, not a formal method for assessing the statistical significance of the between-group differences in adverse experiences and predefined limits of change.

Continuous measures such as changes from baseline in laboratory, vital signs, and ECG parameters that are not pre-specified as Tier-1 endpoints will be considered Tier 3 safety parameters. Summary statistics for baseline, on-treatment, and change from baseline values will be provided by treatment group in table format. In addition, summary statistics for the difference between treatment groups will also be provided, along with nominal p-values for between-group differences. Mean change from baseline over time will be plotted with the corresponding standard errors.

To properly account for the potential difference in follow-up time between the study arms, which is expected to be longer in the MK-3475 arm, an important analysis of Tier 1 AE and Grade 3-5 AE will be based on the time to first event using the same time-to-event analysis methods as for OS (i.e., the stratified log-rank test will be used for testing the time to AEs, and the stratified Cox model with Efron's tie handling method will be used for estimating the hazard ratio and its 95% confidence interval). For other AEs with potentially differential follow-up time, such analysis may also be explored.

In addition, the p-value and 95% confidence interval for between-treatment difference in the percentage of subjects with Grade 3-5 AE overall as well as per cycle for the first four cycles, and the between-treatment difference in the Grade 3-5 AE incidence density adjusted for treatment exposure (AE duration is defined as from first dose of study drug to 30 days after last dose of study drug) will be calculated using the stratified Miettinen and Nurminen method [30].

Further, pre-specified adverse events of clinical interest include the following events that are determined to be immune-related by the investigator: 1) Grade $\geq$ 3 diarrhea 2) Grade $\geq$ 2 colitis, 3) Grade $\geq$ 2 pneumonitis, 4) Grade $\geq$ 3 hypo- or hyperthyroidism will be collected as Tier 1 events. P-values and 95% confidence intervals will be provided for between-treatment differences in the percentage of subjects with these events.

Table 10 Analysis Strategy for Safety Parameters

Safety Tier	Safety Endpoint	p-Value	95% CI for Treatment Comparison	Descriptive Statistics
Tier 1	Gr ≥ 3 Diarrhea with a potential immunologic etiology	X	X	X
	Gr ≥ 2 Colitis with a potential immunologic etiology	X	X	X
	Gr ≥ 2 Pneumonitis with a potential immunologic etiology	X	X	X
	Gr ≥ 3 Hypo- or hyperthyroidism with a potential immunologic etiology	X	X	X
Tier 2	Any AE		X	X
	Any Grade 3-5 AE		X	X
	Any Serious AE		X	X
	Onset and Duration of First Grade 3-5 AE		X	X
	Any Drug-Related AE		X	X
	Any Serious and Drug-Related AE		X	X
	Any Grade3-5 and Drug-Related AE		X	X
	Dose Modification due to AE		X	X
	Discontinuation due to AE		X	X
	Death		X	X
	Specific AEs, SOCs (including ≥4 of subjects in one of the treatment groups)		X	X
Tier 3	Specific AEs, SOCs (incidence <4 of subjects in all of the treatment groups)			X
	Change from Baseline Results (Labs, ECGs, Vital Signs)			X

8.2.5.3 Summaries of Baseline Characteristics, Demographics, and Other Analyses

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.

The reasons for exclusion from the ITT population (if any) will be summarized.

8.2.6 Multiplicity

The overall type I error is strongly controlled at 2.5% (one-sided) with 0.35% allocated to PFS and 2.15% allocated to OS hypothesis.

For PFS, 0.25% will be spent at the second interim analysis (primary analysis of PFS) and 0.1% will be spent at the final analysis to capture the long-term PFS effect. At each analysis, the Hochberg step-up procedure will be used for PFS testing in the strongly positive PD-L1 stratum, giving equal weights to the two MK-3475 arms, if neither is discontinued prior to that analysis. At each analysis, a gate-keeping testing procedure will be used for adjustment over the strongly positive PD-L1 stratum and the overall PD-L1 positive population. If both MK-3475 arms demonstrate superior PFS in the strongly positive stratum, PFS will be tested in the overall PD-L1 positive population at the same alpha level.

For OS, 0.5% will be spent at the second interim analysis, and 1.65% will be allocated to the final analysis. The Hochberg step-up procedure will be used for OS testing at each analysis, giving equal weights to the two MK-3475 arms, if neither is discontinued prior to that analysis. At the second interim analysis, a gate-keeping testing procedure will be used for adjustment over the strongly positive PD-L1 stratum and the overall PD-L1 positive population: only if both MK-3475 arms demonstrate superior OS in the strongly positive stratum, will OS be tested sequentially in the overall PD-L1 positive population at the same alpha level. At the final analysis, a Bonferroni correction will be used to adjust for the OS tests in strongly positive PD-L1 stratum and in the overall PD-L1 positive population: the strongly positive PD-L1 stratum and the overall PD-L1 positive population will be tested at $\alpha/2$ each, where α will be between 1.65% and 2.00% and the actual alpha level depends on whether or not both MK-3475 arms are superior in PFS for the overall positive population at the second interim analysis and the final analysis. See Figure 2 for the multiplicity strategy diagram for the study.

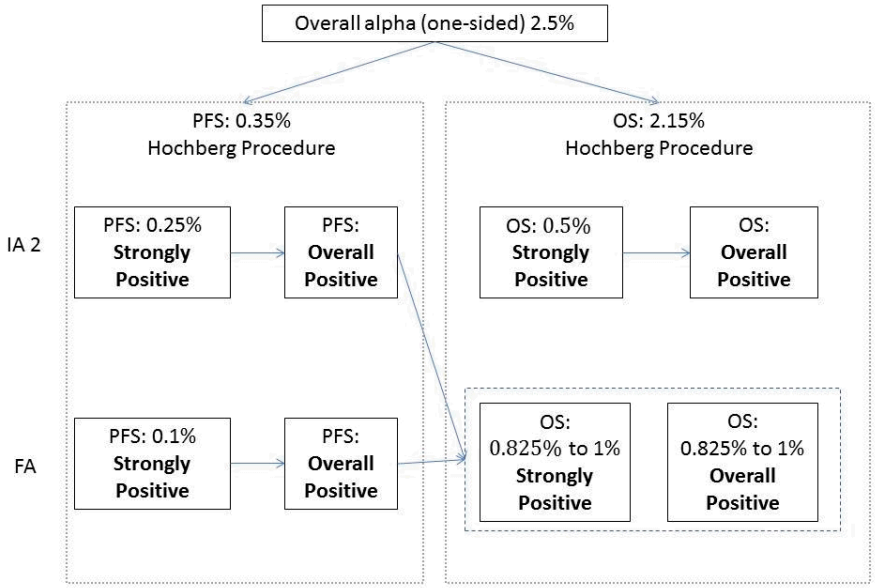


Figure 2 Multiplicity Strategy

8.2.7 Sample Size and Power Calculations

The study will randomize subjects in a 1:1:1 ratio into two MK-3475 arms and one docetaxel arm. The sample size for subjects with strongly positive PD-L1 is targeted at approximately 460, and the overall sample size for this study is projected to be approximately 920.

The study is event driven (i.e., the number of subjects and follow-up time are subject to change but the number of events is not) and will complete after approximately 200 deaths have been observed across three arms from the strongly positive PD-L1 stratum. The sample size calculation is based on the following assumptions for subjects in the strongly positive PD-L1 stratum: 1) overall survival follows an exponential distribution with a median of 9 months in the control arm, 2) the hazard ratio between MK-3475 and control is 0.60, 3) an enrollment period of 16 months and a minimum of 8 months follow-up after enrollment completion, 4) a dropout rate of 2% in 12 months. The assumed median overall survival time of 9 months for subjects treated with docetaxel is based on historical data on docetaxel [18], and the possible positive prognostic nature of high PD-L1 expression levels. The median OS in docetaxel could be greater or less than 9 months in patients with strongly positive PD-L1 expression if PD-L1 expression is prognostic for docetaxel.

PFS analysis: the primary PFS analysis will be carried out at the second interim analysis, which occurs after approximately 175 PFS events across three arms have accumulated in the strongly positive PD-L1 stratum. An alpha of 0.250% will be allocated to PFS in the strongly positive stratum at this analysis. This interim analysis has >85% power to detect a 0.5 hazard ratio at alpha=0.250% in the strongly positive PD-L1 stratum using the Hochberg procedure

when there are 123 PFS events between one MK arm and the docetaxel arm under the alternative hypothesis.

An analysis of long-term PFS effect will be carried out at the final analysis at 0.1% alpha (one-sided) in the strongly positive PD-L1 stratum. It is expected that approximately 345 PFS events would have been observed across three arms (approximately 240 PFS events between one MK arm and the docetaxel arm) in the strongly positive PD-L1 stratum at this analysis under the alternative hypothesis. This will give >95% power to detect a 0.5 hazard ratio, and 88% power to detect a 0.6 hazard ratio at alpha=0.1%.

OS analysis: Two analyses of OS will be carried out: the first OS analysis will be carried out at the second interim analysis, by which time approximately 120 deaths are expected to have been observed across three arms; the final OS analysis will be carried out when approximately 200 deaths have occurred across three arms in the strongly positive PD-L1 stratum. At the second interim analysis, with approximately 84 deaths between two treatment arms, the study has at least 47% (32%) power to detect a 0.55 (0.60) hazard ratio at alpha=0.5% (one-sided) in the PD-L1 strongly positive stratum; at the final analysis, with approximately 140 deaths between two treatment arms, the study has at least 81% (65%) power to detect a 0.55 (0.60) hazard ratio at alpha=0.825% (one-sided) in the PD-L1 strongly positive stratum under a Hochberg procedure for the two MK-3475 vs. docetaxel comparisons. Figure 3 shows the study power for OS superiority in the PD-L1 strongly positive stratum at the second interim and final analysis. Approximately 550 deaths are expected to have been observed across three arms in the overall PD-L1 positive population at the final analysis. With 378 death observed between two treatment arms, the study has at least 80% power to detect a 0.70 hazard ratio at alpha=0.825% (one-sided) in the overall PD-L1 positive population using Hochberg procedure for the two comparisons versus docetaxel. Figure 4 shows the study power for OS superiority in the overall PD-L1 positive population at the final analysis. Details on the final analysis are summarized in section 8.2.9.3.

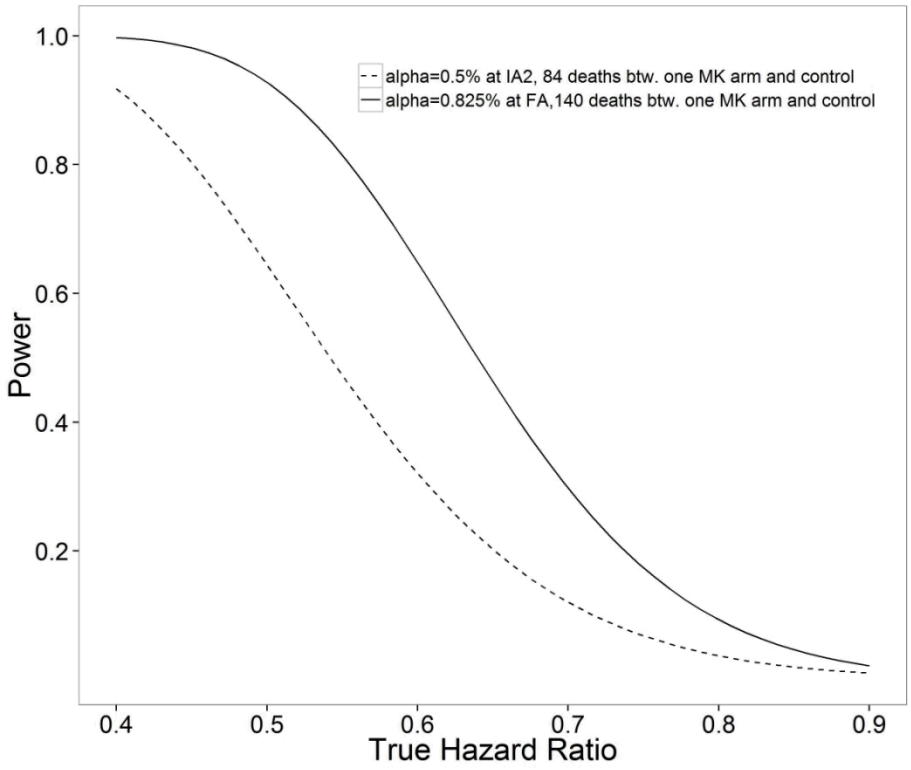


Figure 3 Power for OS Superiority in the PD-L1 Strongly Positive Stratum under Various Hazard Ratios using Hochberg Procedure at the Second Interim Analysis (IA2) and the Final Analysis (FA)

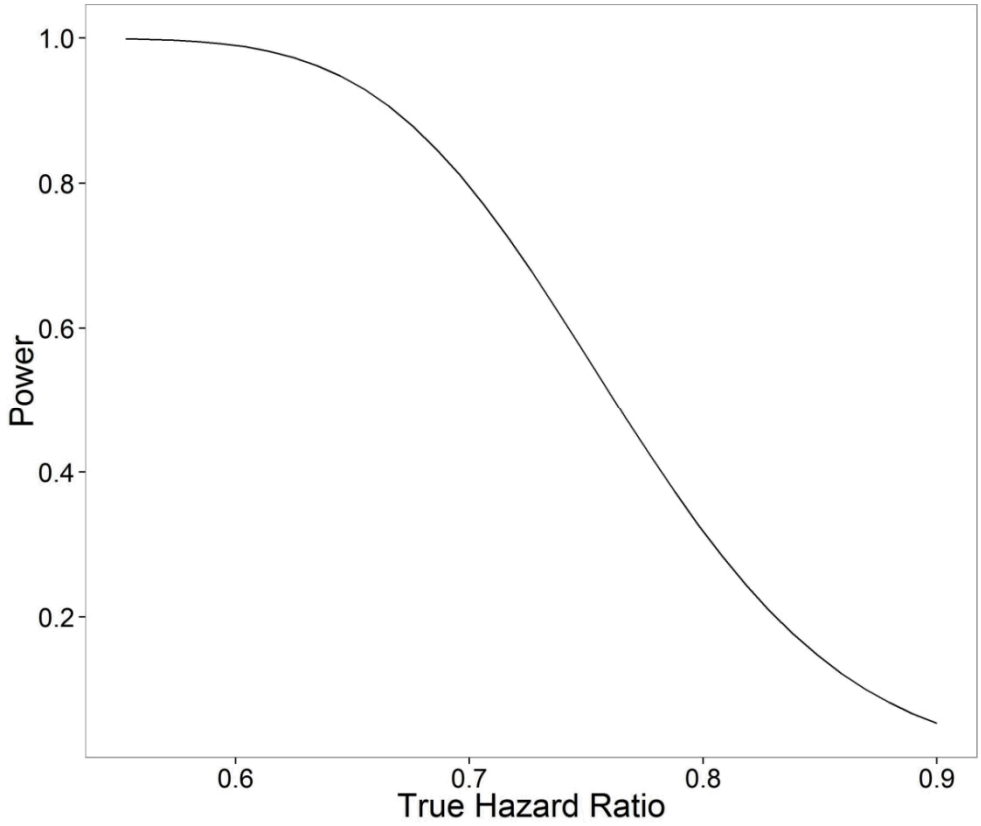


Figure 4 Power for OS Superiority in the Overall PD-L1 Positive Population under Various Hazard Ratios using Hochberg Procedure at the Final Analysis (378 deaths between two groups)

8.2.8 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 endpoint will be estimated and plotted within each category of the following classification variables:

- Age category (≤65 vs. >65 years)
- Sex (female, male)
- Race (white, non-white)
- ECOG status (0 vs. 1)
- Geographic region of enrolling site (East Asia, non-East Asia)
- Ethnicity (East Asian, non-East Asian)

- Previous chemotherapy regimen (types with greater than 10% subjects in the control group)
- ALK translocation status (translocated vs. wild type)
- EGFR mutation status (wild type vs. mutant)
- **Age of tumor specimen (archival vs. new)**

The consistency of the treatment effect will be assessed descriptively via summary statistics by category for the classification variables listed above. These subgroup analyses will be carried out in both the strongly positive PD-L1 stratum and the overall positive population. The treatment effect in the subgroup of subjects who were enrolled after the PD-L1 strong/weak cut point became available will also be explored.

8.2.9 Interim Analyses

There are two planned interim analyses. Enrollment will not be put on hold during the interim analyses.

First Interim Analysis

The first IA occurs after the first 120 randomized subjects in the strongly positive PD-L1 stratum have a minimum of 3 months follow-up (approximately 10 months after randomization of the first subject).

The primary objective of this analysis is to stop the trial or discontinue one MK-3475 arm if the overall unconfirmed and confirmed response data per RECIST 1.1 indicate futility. The decision rules are nonbinding, and are subject to modification based on emerging external data. As guidance, if the p-value of the difference of response rates (MK-3475 vs. docetaxel) is greater than 20% (two-sided) in the strongly positive PD-L1 stratum for both MK-3475 arms, the study may be terminated. A <13% difference (e.g., <23% vs. 10% in docetaxel for both MK arms) will approximately meet the criterion for study discontinuation. In addition, if the p-value of the difference of response rates between the two MK-3475 arms is less than 2.5% (two-sided) in the strongly positive stratum, the MK-3475 arm with the lower response rate may be discontinued from the trial. A< 23% difference (e.g., 33% vs. 10%) will approximately meet the criterion for discontinuing one of the MK-3475 arms. The futility stopping criteria are non-binding and the totality of the data including tumor volumetric change, PFS, OS and safety data based on these subjects as well as all enrolled subjects will be reviewed by the DMC to facilitate decisions. See Table 11 for the operating characteristics at the first IA.

Table 11 Operating Characteristics at IA1 for Futility Stopping (With 40 subjects/arm in the strongly positive PD-L1 stratum)

True Response Rate	Prob (Observed RR difference >23%)	Prob (Observed RR difference >13%)
40%	76%	96%
35%	59%	90%
30%	39%	78%
25%	21%	60%
20%	8%	38%
15%	2%	19%
10% response rate is assumed for the other treatment.		

There is no intention to stop the trial for efficacy at this analysis.

Second Interim Analysis

The second interim analysis will be conducted after approximately 175 PFS events have been observed across three arms from the strongly positive PD-L1 stratum (approximately 123 PFS events between one MK-3475 arm and the docetaxel arm under the alternative hypothesis). The primary objective of this interim analysis is to demonstrate superiority in PFS for subjects with strongly positive PD-L1 expression at the 0.25% significance level. PFS is determined by RECIST 1.1 based on blinded independent radiologists' review. The Hochberg step-up procedure will be used for PFS testing. If the p-value for both MK arms is <0.25%, both MK arms are superior to docetaxel arm in PFS; if the least significant (larger) p-value is >0.25% then the most significant (smaller) p-value needs to be compared with 0.125% (or 0.25%/2). A p-value of 0.25% (one-sided) for PFS approximately corresponds to an empirical hazard ratio of 0.603 (or approximately >2.0 months of improvement if median PFS in docetaxel is 3 months) and a p-value of 0.125% (or 0.25%/2) approximately corresponds to an empirical hazard ratio of 0.580 (or approximately >2.2 months of improvement if median PFS in docetaxel is 3 months). A positive finding on PFS may lead to regulatory filing for drug approval upon discussion with regulatory agencies. There is no intention to change the conduct of study based on the PFS at this analysis. If both MK-3475 arms demonstrate superior PFS in the strongly positive stratum, PFS will be tested in the overall PD-L1 positive population at the same alpha level, using the same Hochberg step-up procedure.

At the second interim analysis, OS will also be tested at the 0.5% level. Approximately 120 deaths will be observed across three arms in the strongly positive PD-L1 stratum. The Hochberg step-up procedure will be used for OS testing. Only after both MK-3475 arms demonstrate superior OS to docetaxel in the strongly positive stratum, will OS be tested sequentially in the overall PD-L1 positive population at the same alpha level. Based on the Hochberg procedure, if the p-value for both MK arms is <0.5%, both MK arms are superior to the docetaxel arm in OS; if the least significant (larger) p-value is >0.5% then the most significant (smaller) p-value needs to be compared with 0.25% (or 0.5%/2). With 120 OS events across three arms, approximately 84 OS events are expected to be between one MK-

3475 and docetaxel arm under the alternative hypothesis. At 0.5% alpha, both MK arms are superior to docetaxel in OS if both MK arms have an observed hazard ratio of approximately 0.570 or less (> 6.8 months of improvement when the median OS in docetaxel is 9 months); only one MK arm is superior to docetaxel in OS if one MK arm has an observed HR of approximately 0.542 or less (>7.6 months of improvement when median OS in docetaxel is 9 months) but the other MK arm has an observed HR of > 0.570. If both MK-3475 arms demonstrate superior OS in the strongly positive stratum, OS will be tested in the overall PD-L1 positive population at the same alpha level, using the same Hochberg step-up procedure.

Final Analysis

The final analysis will be carried out when approximately 200 deaths have occurred across three arms in the strongly PD-L1 positive stratum (approximately 140 deaths between one MK-3475 arm and the docetaxel arm under the alternative hypothesis).

If both MK-3475 arms proceed to study completion, the Hochberg step-up procedure will be used for OS and PFS testing (MK vs. docetaxel) at the final analysis, giving equal weights to the two MK- 3475 arms.

Alpha for OS at the final analysis (α_{os}) will be between 1.65% and 2.00%, and the actual alpha level depends on whether or not both MK-3475 arms demonstrate superiority in PFS for the overall PD-L1 positive population at the second interim analysis and the final analysis. A Bonferroni procedure will be used for the adjustment over the strongly positive PD-L1 stratum and the overall PD-L1 positive population. OS will be tested in the PD-L1 strongly positive stratum and the overall PD-L1 positive population each at the same adjusted alpha level ($\alpha_{os}/2$).

Based on the Hochberg procedure, if the p-value for both MK arms is $<\alpha_{os}/2$, both MK arms are superior to docetaxel in OS; if the least significant (larger) p-value is $> \alpha_{os}/2$ then the most significant (smaller) p-value needs to be compared with $\alpha_{os}/4$. With 0.825% alpha for OS in PD-L1 strongly positive stratum at the final analysis, both MK-3475 arms are superior to docetaxel if both MK-3475 arms have an observed HR of approximately 0.667 or less for both MK arms (> 4.5 months of improvement in OS); only one MK arm is superior to docetaxel if one MK arm has an observed HR of approximately 0.640 or less (>5.1 months of improvement in OS) but the other MK arm has an observed HR of > 0.667. Table 12 shows the empirical bars for a positive OS in PD-L1 strongly positive stratum at the final analysis. Similarly, Table 13 shows the empirical bars for a positive OS in the Overall PD-L1 positive population at the final analysis.

Table 12 Approximate empirical bars for a positive OS in the PD-L1 strongly positive stratum at the final analysis based on outcomes in PFS for the overall PD-L1 positive population

IA2 (alpha = 0.25% for PFS)	Final analysis (alpha = 0.1% for PFS)	Nominal alpha for OS in PD-L1 strong positive	Both MK arms are superior in OS at FA Empirical hazard ratio[1] (empirical median improvement in month[2])	Only One MK arm is superior in OS at FA Empirical hazard ratio[1] (empirical median improvement in month[2])
At least one MK arm does not have superior PFS	At least one MK arm does not have superior PFS	0.825%	0.667 (4.5 m.)	0.640 (5.1 m.)
At least one MK arm does not have superior PFS	Both MK arms have superior PFS	0.875%	0.669 (4.4 m.)	0.642 (5.0 m.)
Both MK arms have superior PFS	At least one MK arm does not have superior PFS	0.95%	0.673 (4.4 m.)	0.645 (5.0 m.)
Both MK arms have superior PFS	Both MK arms have superior PFS	1.00%	0.675 (4.3 m)	0.647 (4.9 m.)

[1] Observed treatment effect which may lead to statistical significance based on 140 deaths between one MK arm and docetaxel arm in the PD-L1 strongly positive stratum, and half of allocated alpha as a conservative estimate under Hochberg procedure
[2] Median survival for docetaxel is assumed to be 9 months

Table 13 Approximate empirical bars for a positive OS in the overall PD-L1 positive population at the final analysis based on outcomes in PFS for the overall PD-L1 positive population

IA2 (alpha = 0.25% for PFS)	Final analysis (alpha = 0.1% for PFS)	Nominal alpha for OS in PD-L1 strong positive	Both MK arms are superior in OS at FA Empirical hazard ratio[1] (empirical median improvement in month[2])	Only One MK arm is superior in OS at FA Empirical hazard ratio[1] (empirical median improvement in month[2])
At least one MK arm does not have superior PFS	At least one MK arm does not have superior PFS	0.825%	0.781 (2.5 m.)	0.762 (2.8 m.)
At least one MK arm does not have superior PFS	Both MK arms have superior PFS	0.875%	0.783 (2.5 m.)	0.764 (2.8 m.)
Both MK arms have superior PFS	At least one MK arm does not have superior PFS	0.95%	0.786 (2.5 m.)	0.766 (2.8 m.)
Both MK arms have superior PFS	Both MK arms have superior PFS	1.00%	0.787 (2.4 m.)	0.767 (2.7 m.)

[1] Estimated treatment effect which may lead to statistical significance based on 378 deaths between one MK arm and docetaxel arm in the overall PD-L1 positive population
[2] Median survival for docetaxel is assumed to be 9 months

8.2.10 Compliance (Medication Adherence)

Drug accountability data for trial treatment will be collected during the study. Compliance with trial treatment administration will be measured by subjects: 1) receiving unscheduled study agent infusions/injections; 2) missing an infusion/injection. Numbers and percentages of subjects and infusion/injection visits with any deviation in these measures will be reported for the ITT population.

8.2.11 Extent of Exposure

The extent of exposure will be summarized as duration of treatment in cycles. Dose intensity will also be summarized as appropriate.

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 14.

Table 14 Product Description

Product Name & Potency	Dosage Form
MK-3475 50 mg	Lyophilized Powder for Injection
MK-3475 100 mg/ 4 mL	Solution for Injection
Docetaxel 80 mg/ 4 mL	Solution for Injection

All other supplies not indicated in Table 14 above will be provided centrally by the Sponsor or locally by the trial site or subsidiary, 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 will be responsible for recording the lot number, manufacturer and expiry date of any locally purchased product.

9.2 Packaging and Labeling Information

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

Vials will be provided in an open label fashion for subject dosing.

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, potency) is included in the label text; random code/disclosure envelopes or lists are not provided.

9.4 Storage and Handling Requirements

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

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

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

9.5 Returns and Reconciliation

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

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

9.6 Standard Policies

Trial site personnel will have access to a central electronic randomization system (IVRS/IWRS system) to allocate subjects, to assign drug 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.

10.2 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 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 discarding 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 by the Sponsor.

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.

11.0 LIST OF REFERENCES

[1] Disis ML. Immune regulation of cancer. J Clin Oncol 2010;28(29):4531-8.

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

[3] Hunder NN, Wallen H, Cao J, Hendricks DW, Reilly JZ, Rodmyre R, et al. Treatment of metastatic melanoma with autologous CD4+ T cells against NY-ESO-1. N Engl J Med 2008;358(25):2698-703.

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

[5] Okazaki T, Maeda A, Nishimura H, Kurosaki T, Honjo T. PD-1 immunoreceptor inhibits B cell receptor-mediated signaling by recruiting src homology 2-domain-containing tyrosine phosphatase 2 to phosphotyrosine. Proc Natl Acad Sci U S A 2001;98(24):13866-71.

[6] Zhang X, Schwartz J-CD, Guo X, Bhatia S, Cao E, Chen L, et al. Structural and functional analysis of the costimulatory receptor programmed death-1. Immunity 2004;20:337-47.

[7] Chemnitz JM, Parry RV, Nichols KE, June CH, Riley JL. SHP-1 and SHP-2 associate with immunoreceptor tyrosine-based switch motif of programmed death 1 upon primary human T cell stimulation, but only receptor ligation prevents T cell activation. J Immunol 2004;173:945-54.

[8] Sheppard K-A, Fitz LJ, Lee JM, Benander C, George JA, Wooters J, et al. PD-1 inhibits T-cell receptor induced phosphorylation of the ZAP70/CD3zeta signalosome and downstream signaling to PKCtheta. FEBS Lett. 2004;574:37-41.

[9] Riley JL. PD-1 signaling in primary T cells. Immunol Rev 2009;229:114-25.

[10] Parry RV, Chemnitz JM, Frauwirth KA, Lanfranco AR, Braunstein I, Kobayashi SV, et al. CTLA-4 and PD-1 receptors inhibit T-cell activation by distinct mechanisms. Mol Cell Biol 2005;25(21):9543-53.

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

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

[13] Pölcher M, Braun M, Friedrichs N, Rudlowski C, Bercht E, Fimmers R, et al. Foxp3(+) cell infiltration and granzyme B(+)/Foxp3(+) cell ratio are associated with outcome in neoadjuvant chemotherapy-treated ovarian carcinoma. Cancer Immunol Immunother 2010;59(6):909-19.

[14] Suzuki H, Chikazawa N, Tasaka T, Wada J, Yamasaki A, Kitaura Y, et al. Intratumoral CD8+ T/FOXP3+ cell ratio is a predictive marker for survival in patients with colorectal cancer. Cancer Immunol Immunother 2010;59:653-61.

[15] Chew V, Tow C, Teo M, Wong HL, Chan J, Gehring A, et al. Inflammatory tumor microenvironment is associated with superior survival in hepatocellular carcinoma patients. J Hepatol 2010;52:370-9.

[16] Liotta F, Gacci M, Frosali F, Querci V, Vittori G, Lapini A, et al. Frequency of regulatory T cells in peripheral blood and in tumour-infiltrating lymphocytes correlates with poor prognosis in renal cell carcinoma. BJU Int 2011;107(9):1500-6.

[17] Fossella FV, DeVore R, Kerr RN, Crawford J, Natale RR, Dunphy F, et al. Randomized phase III trial of docetaxel versus vinorelbine or ifosfamide in patients with advanced non-small-cell lung cancer previously treated with platinum-containing chemotherapy regimens [with Erratum]. J Clin Oncol 2000;18:2354-62.

[18] Hanna N, Shepherd FA, Fossella FV, Pereira JR, de Marinis F, von Pawel J, et al. Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy. J Clin Oncol 2004;22(9):1589-97.

[19] Scagliotti GV, Parikh P, von Pawel J, Biesma B, Vansteenkiste J, Manegold C, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer. J Clin Oncol 2008;26(21):3543-51.

[20] Garassino MC, Martelli O, Bettini A, Floriani I, Copreni E, Lauricella C, et al. TAILOR: A phase III trial comparing erlotinib with docetaxel as the second-line treatment of NSCLC patients with wild-type (wt) EGFR: Metastatic non-small cell lung cancer [Abstract No. LBA7501]. American Society of Clinical Oncology: 2012 ASCO Annual Meeting, 2012.

[21] Shepherd FA, Dancey J, Ramlau R, Mattson K, Gralla R, O'Rourke M, et al. Prospective randomized trial of docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy. J Clin Oncol 2000;18(10):2095-103.

[22] Hanna N, Shepherd FA, Fossella FV, Pereira JR, De Marinis F, von Pawel J, et al. Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy. J Clin Oncol 2004;22(9):1589-97.

[23] USTAXOTERE (docetaxel) injection concentrate, intravenous infusion (IV). initial U.S. Approval: 1996: 2011.

[24] Ruffini E, Asioli S, Filosso PL, Lyberis P, Bruna MC, Macrì L, et al. Clinical significance of tumor-infiltrating lymphocytes in lung neoplasms. Ann Thorac Surg. 2009 Feb;87(2):365-71; discussion 371-2.

[25] Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 1993;85(5):365-76.

[26] Bergman B, Aaronson NK, Ahmedzai S, Kaasa S, Sullivan M. The EORTC QLQ-LC13: a modular supplement to the EORTC core quality of life questionnaire (QLQ-C30) for use in lung cancer clinical trials. Eur J Cancer 1994;30A(5):635-42.

[27] Fallowfield LJ, Harper P. Health-related quality of life in patients undergoing drug therapy for advanced non-small-cell lung cancer. Lung Cancer 2005;48(3):365-77.

[28] EuroQol Group. EuroQol - a new facility for the measurement of health-related quality of life. Health Policy. 1990 Dec;16(3):199-208.

[29] Bottomley A, Efficace F, Thomas R, Vanvoorden V, Ahmedzai SH. Health-related quality of life in non-small-cell lung cancer: Methodologic issues in randomized controlled trials. J Clin Oncol 2003;21(15):2982-92.

[30] Miettinen O, Nurminen M. Comparative analysis of two rates. Stat Med 1985;4:213-26.

[31] Robins JM, Tsiatis AA. Correcting for non-compliance in randomized trials using rank preserving structural failure time models. Commun Stat-Theor M 1991;20(8):2609-31.

[32] Finkelstein DM. A proportional hazards model for interval-censored failure time data. Biometrics 1986;42:845-54.

12.0APPENDICES

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

- **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.

- **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.

- **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

1. 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.

2. 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.

3. 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.

4. 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

1. 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.

2. 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.

3. 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 response.2

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

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research

The DNA and leftover tumor tissue specimen(s) collected in the current trial will be used to study various causes for how subjects may respond to a drug. The DNA and leftover tumor tissue specimen(s) collected during the main study 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 enters and is removed by the body, how a drug works, other pathways a drug may interact with, or other aspects of disease.

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

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.

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

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

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

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

c. eCRF Documentation for Future Biomedical Research Specimens

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

d. Future Biomedical Research Specimen Collections

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

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

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 writing to 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.

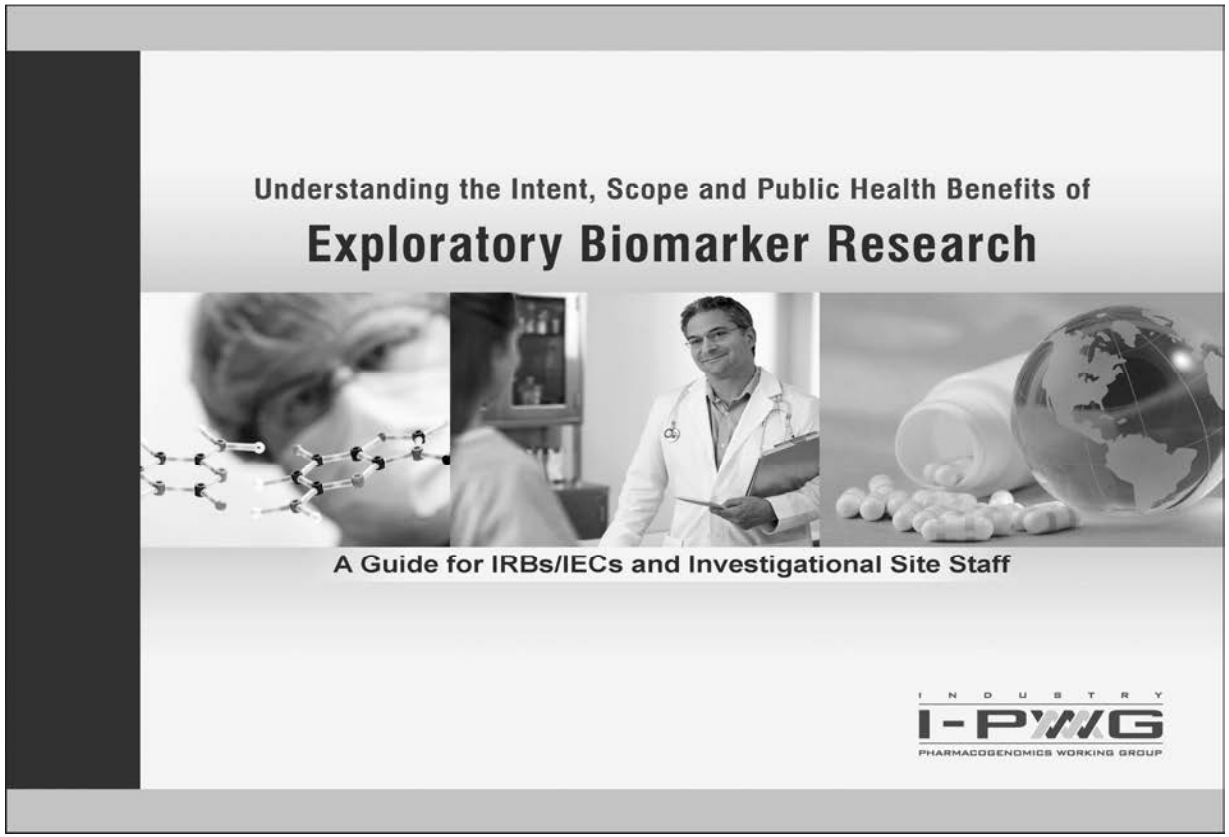
13. Questions

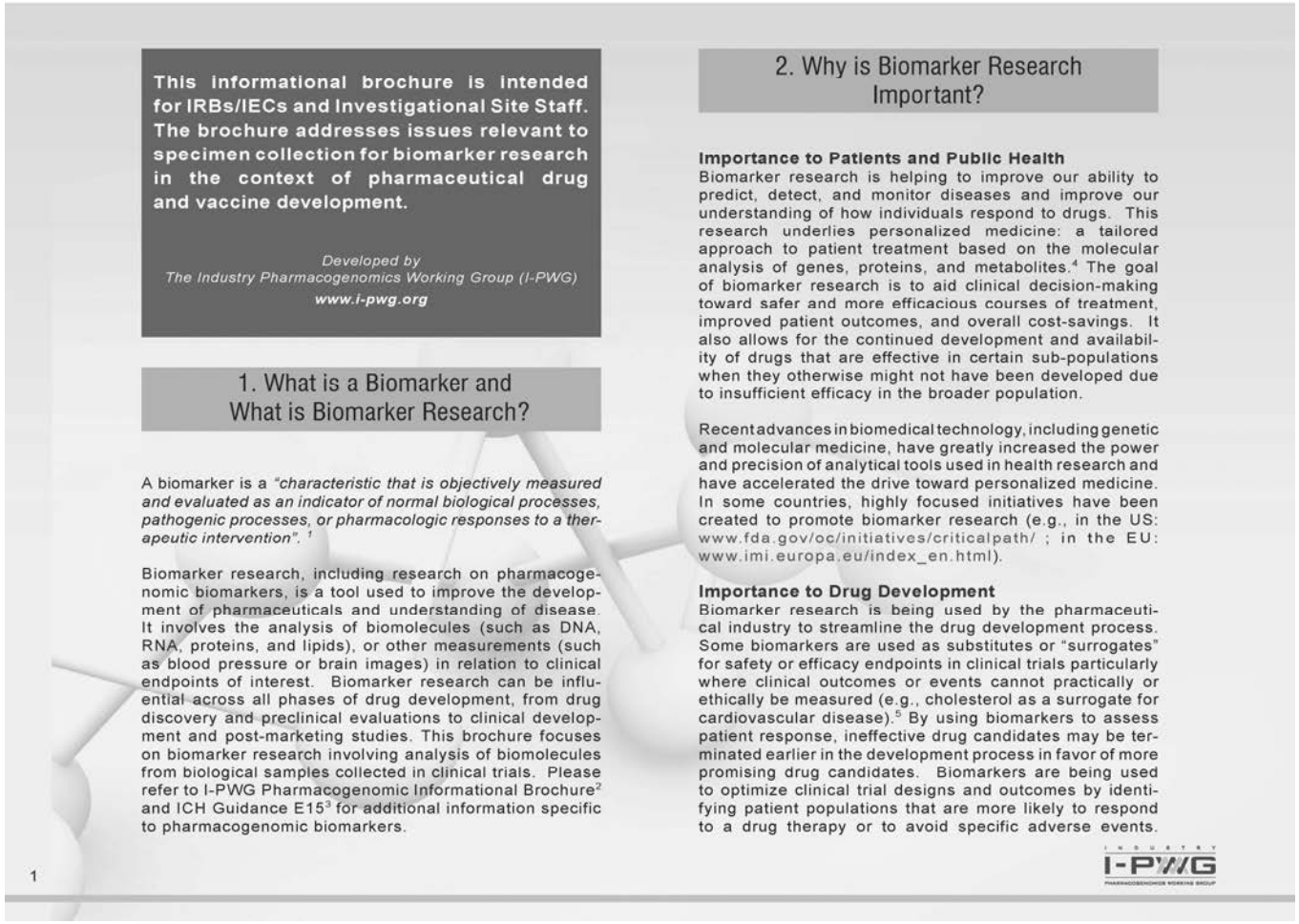
Any questions related to the future biomedical research should be e-mailed directly to clinical.specimen.management@merck.com.

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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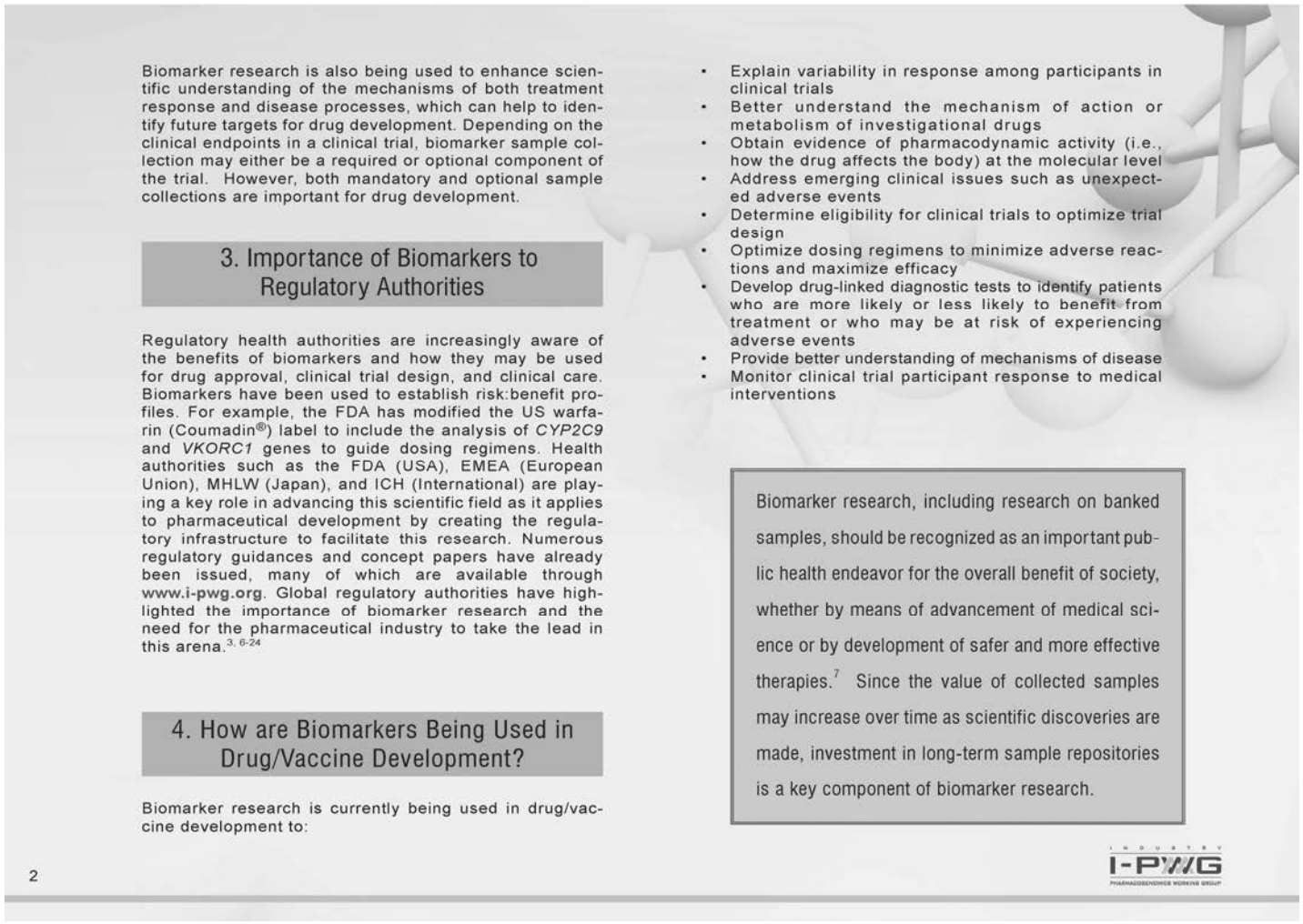

Biomarker research is also being used to enhance scientific understanding of the mechanisms of both treatment response and disease processes, which can help to identify future targets for drug development. Depending on the clinical endpoints in a clinical trial, biomarker sample collection may either 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.[28-31]

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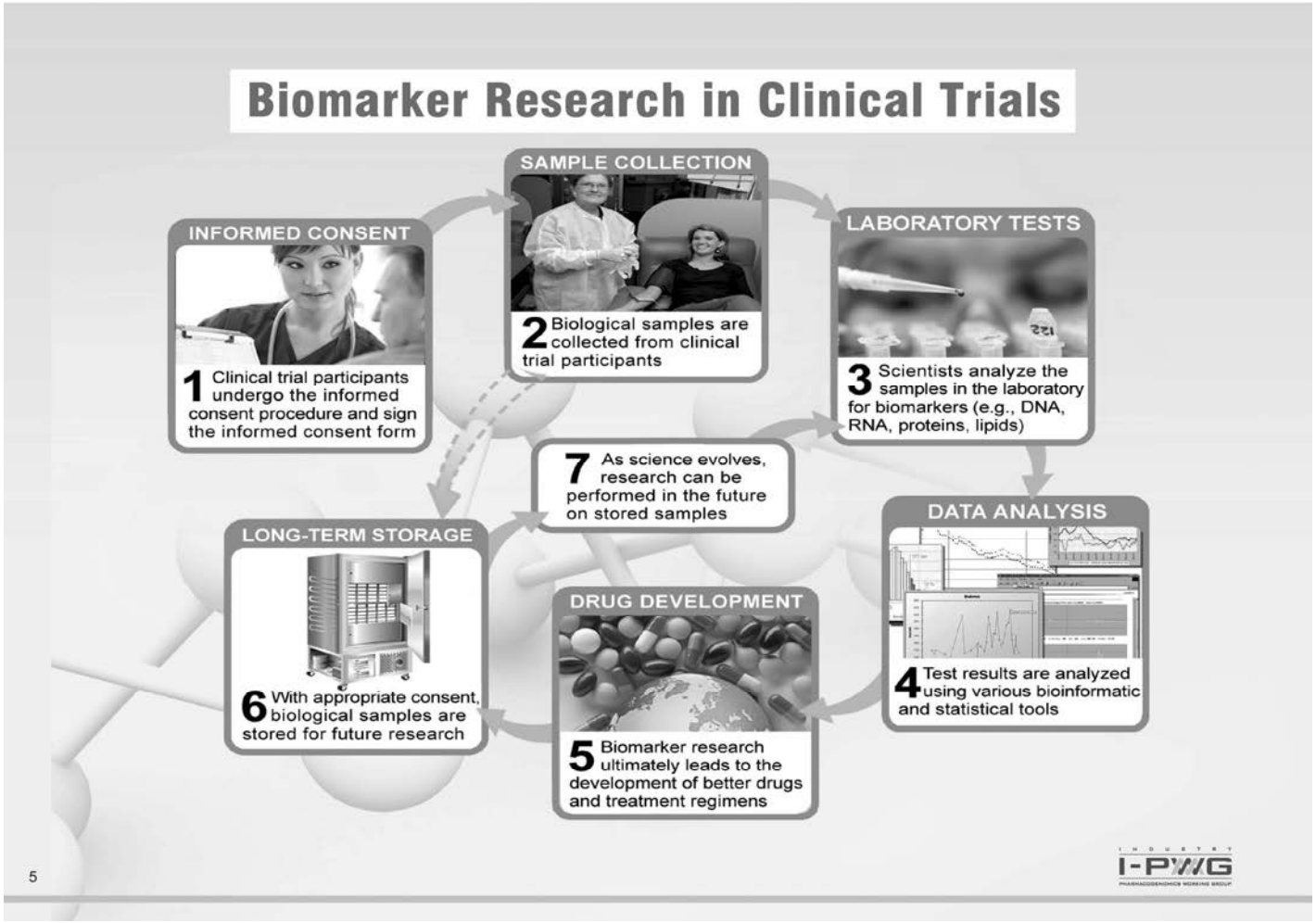
Biomarker Research in Clinical Trials
SAMPLE COLLECTION
2 Biological samples are collected from clinical trial participants
LABORATORY TESTS
3 Scientists analyze the samples in the laboratory for biomarkers (e.g., DNA, RNA, proteins, lipids)
INFORMED CONSENT
1 Clinical trial participants undergo the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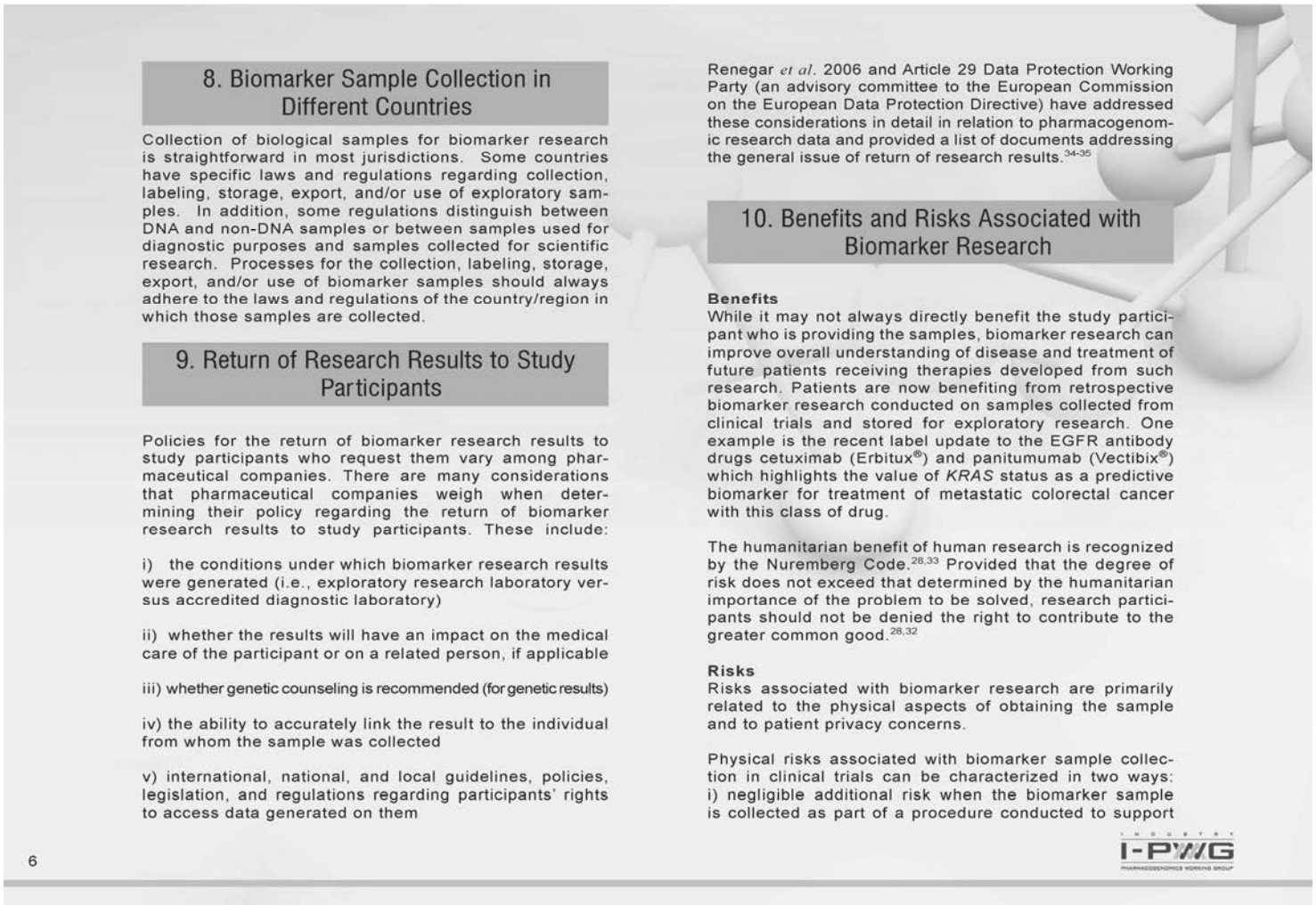
8. Biomarker Sample Collection in Different Countries
Collection of biological samples for biomarker research is straightforward in most jurisdictions. Some countries have specific laws and regulations regarding collection, labeling, storage, export, and/or use of exploratory samples. In addition, some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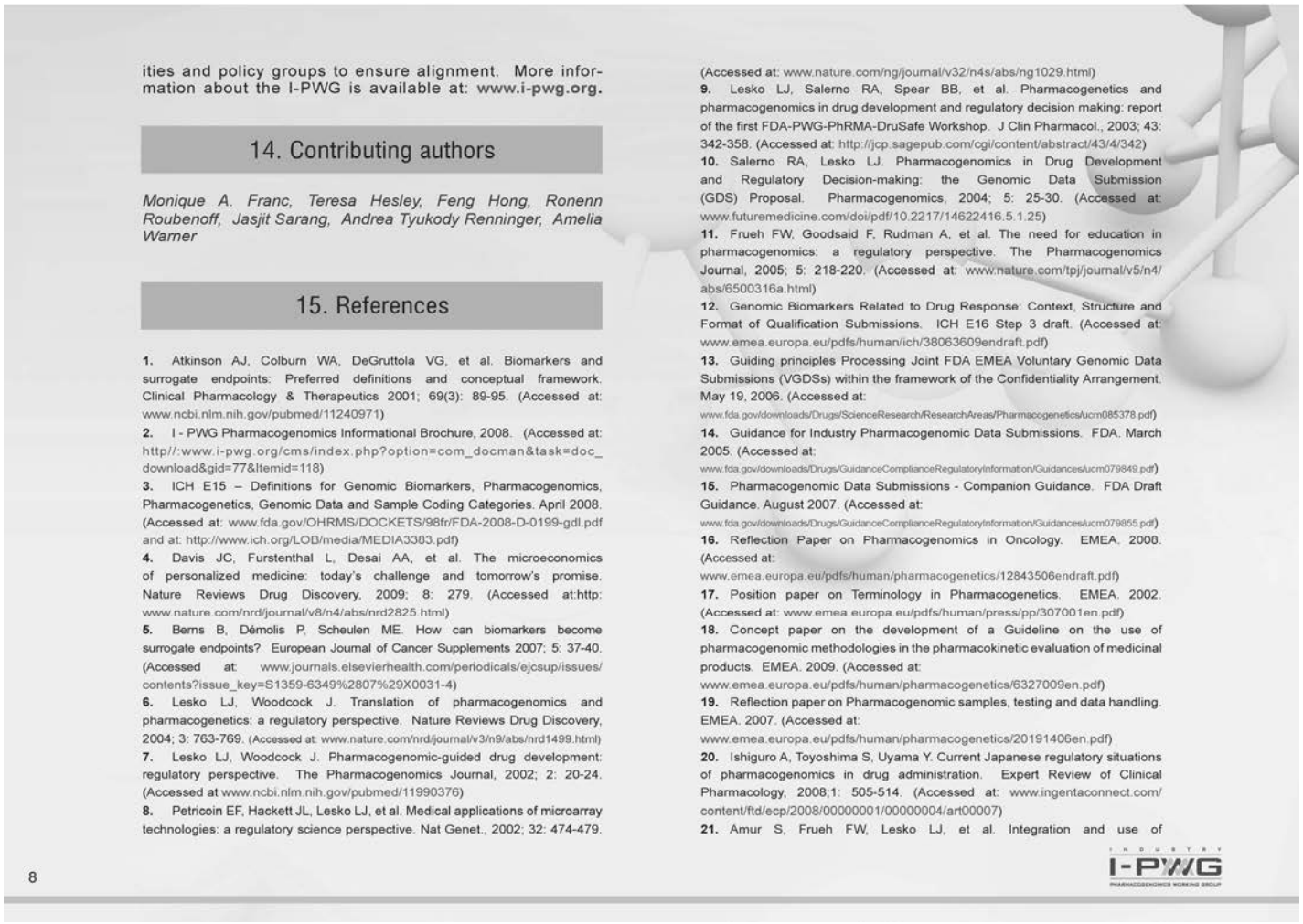

ities and policy groups to ensure alignment. More information about the I-PWG is available at: www.i-pwg.org.

14. Contributing authors

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

15. References

1. Atkinson AJ, Colburn WA, DeGruttola VG, et al. Biomarkers and surrogate endpoints: Preferred definitions and conceptual framework. Clinical Pharmacology & Therapeutics 2001; 69(3): 89-95. (Accessed at: www.ncbi.nlm.nih.gov/pubmed/11240971)

2. I - PWG Pharmacogenomics Informational Brochure, 2008. (Accessed at: http//:www.i-pwg.org/cms/index.php?option=com_docman&task=doc_download&gid=77&Itemid=118)

3. ICH E15 – Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories. April 2008. (Accessed at: www.fda.gov/OHRMS/DOCKETS/98fr/FDA-2008-D-0199-gdl.pdf and at: http://www.ich.org/LOB/media/MEDIA3303.pdf)

4. Davis JC, Furstenthal L, Desai AA, et al. The microeconomics of personalized medicine: today's challenge and tomorrow's promise. Nature Reviews Drug Discovery, 2009; 8: 279. (Accessed at:http: www.nature.com/nrd/journal/v8/n4/abs/nrd2825.html)

5. Berns B, Démolis P, Scheulen ME. How can biomarkers become surrogate endpoints? European Journal of Cancer Supplements 2007; 5: 37-40. (Accessed at: www.journals.elsevierhealth.com/periodicals/ejcsup/issues/contents?issue_key=S1359-6349%2807%29X0031-4)

6. Lesko LJ, Woodcock J. Translation of pharmacogenomics and pharmacogenetics: a regulatory perspective. Nature Reviews Drug Discovery, 2004; 3: 763-769. (Accessed at: www.nature.com/nrd/journal/v3/n9/abs/nrd1499.html)

7. Lesko LJ, Woodcock J. Pharmacogenomic-guided drug development: regulatory perspective. The Pharmacogenomics Journal, 2002; 2: 20-24. (Accessed at www.ncbi.nlm.nih.gov/pubmed/11990376)

8. Petricoin EF, Hackett JL, Lesko LJ, et al. Medical applications of microarray technologies: a regulatory science perspective. Nat Genet., 2002; 32: 474-479. (Accessed at: www.nature.com/ng/journal/v32/n4s/abs/ng1029.html)

9. Lesko LJ, Salerno RA, Spear BB, et al. Pharmacogenetics and pharmacogenomics in drug development and regulatory decision making: report of the first FDA-PWG-PhRMA-DruSafe Workshop. J Clin Pharmacol., 2003; 43: 342-358. (Accessed at: http://jcp.sagepub.com/cgi/content/abstract/43/4/342)

10. Salerno RA, Lesko LJ. Pharmacogenomics in Drug Development and Regulatory Decision-making: the Genomic Data Submission (GDS) Proposal. Pharmacogenomics, 2004; 5: 25-30. (Accessed at: www.futuremedicine.com/doi/pdf/10.2217/14622416.5.1.25)

11. Frueh FW, Goodsaid F, Rudman A, et al. The need for education in pharmacogenomics: a regulatory perspective. The Pharmacogenomics Journal, 2005; 5: 218-220. (Accessed at: www.nature.com/tpj/journal/v5/n4/abs/6500316a.html)

12. Genomic Biomarkers Related to Drug Response: Context, Structure and Format of Qualification Submissions. ICH E16 Step 3 draft. (Accessed at: www.emea.europa.eu/pdfs/human/ich/38063609endraft.pdf)

13. Guiding principles Processing Joint FDA EMEA Voluntary Genomic Data Submissions (VGDSs) within the framework of the Confidentiality Arrangement. May 19, 2006. (Accessed at: www.fda.gov/downloads/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm085378.pdf)

14. Guidance for Industry Pharmacogenomic Data Submissions. FDA. March 2005. (Accessed at: www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079849.pdf)

15. Pharmacogenomic Data Submissions - Companion Guidance. FDA Draft Guidance. August 2007. (Accessed at: www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079855.pdf)

16. Reflection Paper on Pharmacogenomics in Oncology. EMEA. 2008. (Accessed at: www.emea.europa.eu/pdfs/human/pharmacogenetics/12843506endraft.pdf)

17. Position paper on Terminology in Pharmacogenetics. EMEA. 2002. (Accessed at: www.emea.europa.eu/pdfs/human/press/pp/307001en.pdf)

18. Concept paper on the development of a Guideline on the use of pharmacogenomic methodologies in the pharmacokinetic evaluation of medicinal products. EMEA. 2009. (Accessed at: www.emea.europa.eu/pdfs/human/pharmacogenetics/6327009en.pdf)

19. Reflection paper on Pharmacogenomic samples, testing and data handling. EMEA. 2007. (Accessed at: www.emea.europa.eu/pdfs/human/pharmacogenetics/20191406en.pdf)

20. Ishiguro A, Toyoshima S, Uyama Y. Current Japanese regulatory situations of pharmacogenomics in drug administration. Expert Review of Clinical Pharmacology, 2008;1: 505-514. (Accessed at: www.ingentaconnect.com/content/ftd/ecp/2008/00000001/00000004/art00007)

21. Amur S, Frueh FW, Lesko LJ, et al. Integration and use of

8

biomarkers in drug development, regulation and clinical practice: A US regulatory practice. Biomarkers Med. 2008; 2, 305-311. (Accessed at: www.ingentaconnect.com/content/fm/bmm/2008/00000002/00000003/art00010?crawler=true)

22. Mendrick DL, Brazell C, Mansfield EA, et al. Pharmacogenomics and regulatory decision making: an international perspective. The Pharmacogenomics Journal. 2006; 6(3), 154-157. (Accessed at: www.nature.com/tpj/journal/v6/n3/abs/6500364a.html)

23. Pendergast MK. Regulatory agency consideration of pharmacogenomics. Exp Biol Med (Maywood). 2008; 233:1498-503. (Accessed at: www.ebmonline.org/cgi/content/abstract/233/12/1498)

24. Goodsaid F, Frueh F. Process map proposal for the validation of genomic biomarkers. Pharmacogenomics., 2006; 7(5):773-82 (Accessed at: www.futuremedicine.com/doi/abs/10.2217/14622416.7.5.773)

25. FDA Table of Valid Genomic Biomarkers in the Context of Approved Drug Labels. (Accessed at: www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm)

26. International Serious Adverse Event Consortium. (Accessed at: www.saeconsortium.org)

27. Predictive Safety Testing Consortium. (Accessed at: www.c-path.org/pstc.cfm)

28. Nuremberg code. (Accessed at: http://ohsr.od.nih.gov/guidelines/nuremberg.html)

29. Declaration of Helsinki. (Accessed at: http://ohsr.od.nih.gov/guidelines/helsinki.html)

30. Belmont report. (Accessed at: http://ohsr.od.nih.gov/guidelines/belmont.html)

31. ICH E6(R1) – Guideline for Good Clinical Practice. June 1996. (Accessed at: www.ich.org/LOB/media/MEDIA482.pdf)

32. Barnes M, Heffernan K. The "Future Uses" Dilemma: Secondary Uses of Data and Materials by Researchers for Commercial Research Sponsors. Medical Research Law & Policy, 2004; 3: 440-450.

33. Eriksson S, Helgesson G. Potential harms, anonymization, and the right to withdraw consent to biobank research. Eur J Hum Genet., 2005; 13:1071-1076. (Accessed at: www.nature.com/ejhg/journal/v13/n9/pdf/5201458a.pdf)

34. Renegar G, Webster CJ, Stuerzebecher S, et al. Returning genetic research results to individuals: points-to-consider. Bioethics 2006; 20: 24-36. (Accessed at: http://www3.interscience.wiley.com/cgi-bin/fulltext/118562753/PDFSTART)

35. Article 29 Data Protection Working Party. (Accessed at: www.ec.europa.eu/justice_home/fsj/privacy/workinggroup/index_en.htm)

36. Human Tissue Act 2004 (UK). (Accessed at: www.opsi.gov.uk/acts/acts2004/en/ukpgaen_20040030_en_1)

37. Genetic Information Nondiscrimination Act. (Accessed at: http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=110_cong_public_laws&docid=f:publ233.110.pdf)

38. Guidance for Sponsors, Clinical Investigators, and IRBs Data Retention When Subjects Withdraw from FDA-Regulated Clinical Trials. FDA October 2008 www.fda.gov/OHRMS/DOCKETS/98fr/FDA-2008-D-0576-gdl.pdf

39. Anderson C, Gomez-Mancilla B, Spear BB, Barnes DM, Cheeseman K, Shaw P, Friedman J, McCarthy A, Brazell C, Ray SC, McHale D, Hashimoto L, Sandbrink R, Watson ML, Salerno RA, on behalf of The Pharmacogenetics Working Group. Elements of Informed Consent for Pharmacogenetic Research; Perspective of the Pharmacogenetics Working Group. Pharmacogenomics Journal 2002;2:284-92. (Accessed at: www.nature.com/tpj/journal/v2/n5/abs/6500131a.html)

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12.4 ECOG Performance Status

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

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

12.5 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 Immune Related Response Criteria

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

Definitions of measurable and non-measurable disease

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

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

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

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

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

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

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

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

Overall response using irRC:

- **Complete Response (irCR):** Complete disappearance of all tumor lesions (whether measureable or not, and no new lesions). CR must be confirmed by repeated, consecutive assessments performed at the next scheduled time point (i.e., every 63 +/- 7 days).

- **Partial Response (irPR):** Decrease in SPD of 50% or greater by a consecutive assessment performed at the next scheduled time point (i.e., every 63 +/- 7 days).

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

- **Progressive Disease (irPD):** At least 25% increase in SPD relative to nadir (minimum recorded tumor burden) Confirmation by a repeat, consecutive assessment performed at the next scheduled time point (i.e., every 63 +/- 7 days).

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

New measurable lesions will be incorporated into the SPD

New non measurable lesions do not define progression but preclude irCR

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

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

REFERENCE

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

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

12.7 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).

12.8 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.

13.0 SIGNATURES

13.1 Sponsor's Representative

TYPED NAME	SIGNATURE	DATE
_____	_____	_____

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	SIGNATURE	DATE
_____	_____	_____