Official Protocol Title:	A Phase I/II Study of MK-3475 (SCH900475) in Combination with Chemotherapy or Immunotherapy in Patients with Locally Advanced or Metastatic Non-Small Cell Lung Carcinoma
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TITLE:

A Phase I/II Study of MK-3475 (SCH900475) in Combination with Chemotherapy or Immunotherapy in Patients with Locally Advanced or Metastatic Non-Small Cell Lung Carcinoma

IND NUMBER: 116833
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DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Amendment 05	20-APR-2020	To extend the duration of the study, update Future Biomedical Research (FBR) language, and change the Follow-up imaging interval.
Amendment 04	18-DEC-2017	To clarify the maximum duration of treatment with MK-3475 in the treatment and crossover phases and maintenance pemetrexed, change MK-3475 dosing in the Second Course Phase to a fixed dose, provide details regarding the management of infusion-related reactions, increase the window for collecting irAEs, and update the timing and procedures for survival status assessment.
Amendment 03	18-APR-2016	To update primary objective and hypothesis, efficacy endpoints, analyses, statistical methods, multiplicity strategy, and sample size and power based on data from Cohort C (Part 1).
Amendment 02	16-APR-2015	To update discontinuation criteria attributed to gefitinib for subjects in Cohort F, and clarify time frames to assess and record adverse events.
Amendment 01	15-OCT-2014	To modify MK-3475 or chemotherapy dose regimen in Cohorts D, E, F, and G based on safety and efficacy information updates.
Original protocol	08-OCT-2013	

SUMMARY OF CHANGES

Overall Rationale for the Amendments:

Amended protocol to extend the duration of the study, update Future Biomedical Research (FBR) language, and change the Follow-up imaging interval.

PRIMARY REASON(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
1.0	Trial Summary	Study duration extended 2 additional years.	To accommodate subjects on extended pemetrexed cycles.
4.2.3.5	Future Biomedical Research	FBR language updated to remove references to “sub-trial”.	To clarify that FBR is not a separate sub-study with reporting.
7.1.1.1.2	Consent and Collection of Specimens for Future Biomedical Research		
12.2	Collection and Management of Specimens for Future Biomedical Research		
6.0	Trial Flow Chart	Follow-up imaging interval changed to every 12 weeks during years 1, 2 and 3, and every 6 months up to the end of year 5.	To update imaging interval in subjects who discontinue trial treatment for reasons other than disease progression or new anticancer therapy.
6.3	Post-Treatment Follow-up Phase		
6.5	Second Course Post-Treatment Follow-up Phase		
7.1.4.3	Tumor Imaging		
7.1.5.3.2	Follow-up Visits		
Throughout	Throughout	Made typographical corrections and minor administrative edits.	To correct typographical errors and clarify intended meaning.

1.0 TRIAL SUMMARY

Abbreviated Title	Phase I/II Study of MK-3475 Combination with Chemotherapy in NSCLC Subjects
Trial Phase	Phase I-II
Clinical Indication	Treatment of Non-Small Cell Lung Cancer
Trial Type	Interventional
Type of control	Active Control without Placebo
Route of administration	Intravenous
Trial Blinding	Unblinded Open-label
Treatment Groups	Part 1: Cohort A – Carboplatin and Paclitaxel plus MK-3475; Cohort B – Carboplatin, Paclitaxel and Bevacizumab plus MK-3475; Cohort C – Carboplatin and Pemetrexed plus MK-3475, Cohort D – Ipilimumab plus MK-3475, Cohort E – Erlotinib plus MK-3475, Cohort F – Gefitinib plus MK-3475. Part 2 – Cohort G – Carboplatin and Pemetrexed plus/minus MK-3475; Cohort H - Ipilimumab plus MK-3475
Number of trial subjects	Approximately 308 subjects will be enrolled.
Estimated duration of trial	The sponsor estimates that the trial will require approximately 84 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 (up to approximately 7 years). After a screening phase of up to 28 days, eligible subjects will receive assigned treatment on Day 1 of each 3-week (Q3W) dosing cycle. Treatment with MK-3475 will continue for a maximum of 35 cycles (approximately 2 years), 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 the trial treatment or procedure requirements or administrative reasons. MK-3475 treated subjects who have been on therapy for ≥ 6 months and who attain a complete response may consider stopping trial treatment. These subjects, as well as those subjects assigned to the MK-3475 arm who stop trial therapy after 35 cycles of study medication for reasons other than disease progression or intolerability, may be eligible for re-treatment with MK-3475 in the Second Course Phase after they have experienced radiographic disease progression at the discretion of the investigator according to the criteria in Section 7.1.5.4. After the end of treatment, each subject will be followed for a minimum of 30 days for adverse event monitoring even if the patient started new antineoplastic treatment (serious adverse events will be collected for up to 90 days following cessation of Sponsor's product, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier). Subjects will have post-treatment follow-up for disease status, including radiographic imaging every 3 months, initiating a non-study cancer treatment and experiencing disease progression, until death, withdrawing consent, or becoming lost to follow-up. Once the subject has achieved the study objective or study has ended, the subject is discontinued from this study and will be enrolled in an extension study to continue protocol defined assessments and treatment. Subjects who may eventually be eligible for crossover who have not yet transitioned to pembrolizumab will be considered for the extension study on a case-by-case basis.

Randomization Ratio	Randomized 1:1 in cohorts A, B, C and G. Not randomized in cohorts D, E, F and H

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 multicenter, open-label, Phase I/II study of intravenous (IV) MK-3475 at 2 dosing schedules in combination with chemotherapy or immunotherapy in subjects with locally advanced or metastatic non-small cell lung cancer (NSCLC). The study is composed of 2 parts. Part 1 of the study will determine the recommended phase II dose (RP2D) for MK-3475 in combination with different chemotherapy and/or immunotherapy regimens. Part 2 includes a randomized comparison of chemotherapy plus or minus MK-3475 based on the doses defined in Part 1, as well as a cohort expanding the ipilimumab cohort from Part 1. Subject's tumors will be screened at baseline for EGFR mutations, EML4 ALK translocation, and PD-L1 expression. Positive tumor PD-L1 expression will not be required for enrollment; however, subjects in Part 2 Cohort G will be stratified based on PD-L1 status. Subjects with squamous cell histology will not be required to be screened for EGFR mutations or ALK translocations and subjects with known EGFR mutations will not be required to be screened for EML4 ALK. Subjects with known KRAS mutation do not need to be tested for EGFR mutations and ALK translocations. For Part 1, cohorts D, E, and F, the investigator will be allowed to select from any of the open cohorts for which the subject is eligible. For Part 1 cohorts A, B and C, the investigator will be allowed to choose the chemotherapy cohort but subjects will be randomized to chemotherapy plus MK-3475 2 mg/kg or chemotherapy plus MK-3475 10 mg/kg. For Part 2, subjects enrolled into cohort G will be randomized at 1:1 ratio to receive Carboplatin and Pemetrexed plus/minus MK-3475 200mg. Subjects assigned to the chemotherapy arm will have the opportunity to crossover to receive MK-3475 monotherapy once they experience progression of disease (PD) defined by RECIST 1.1 and meet all crossover criteria defined by the protocol. Section 7.1.5.5 provides crossover criteria and guidance. Treatment is limited up to 35 cycles for patients who crossover to MK-3475 monotherapy. The Sponsor may elect to add an arm to cohort G based on additional data available from Part 1 of the study. Opening of cohort H will be determined by the Sponsor after a careful review of available safety and efficacy data from cohort D.

The following applies to all subjects enrolled in Parts 1 and 2. Subjects will be evaluated every 6 weeks (42 ± 7 days) for the first 18 weeks followed by every 9 weeks in Year 1 and every 12 weeks subsequently with radiographic imaging to assess response to treatment, until the subject experiences PD or initiates a new anticancer therapy. All imaging obtained from Part 2 will be submitted for potential independent radiologists' review who will assess the images using Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 for determination

of objective 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 will continue for 35 cycles (approximately 2 years) from the date the first dose has been administered, documented disease progression (investigators may elect to continue MK-3475 treatment beyond progression in specific circumstances outlined in Sections 5.8, and 5.12), 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 RECIST 1.1 may consider stopping trial treatment. These subjects, as well as those subjects assigned to the MK-3475 arm who stop trial therapy after 35 cycles for reasons other than disease progression or intolerability, may be eligible for re-treatment with MK-3475 in the Second Course Phase (for up to 17 cycles) after they have experienced radiographic disease progression at the discretion of the investigator according to the criteria in Section 7.1.5.4. Response or progression in the Second Course Phase will not count towards the ORR and PFS of the primary endpoint in this trial.

After the end of treatment, each subject will be followed for a minimum of 30 days for adverse event monitoring even if the patient started new antineoplastic treatment (serious adverse events will be collected for up to 90 days following cessation of Sponsor's product, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier). 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.

Subjects may have the opportunity to transition to a pembrolizumab extension study if available in the future after closure of this study.

Participation in this trial will be dependent upon supplying tumor tissue from either a newly obtained formalin-fixed specimen, or an older formalin-fixed, paraffin-embedded specimen from locations not radiated prior to biopsy. Newly obtained formalin-fixed specimens are strongly encouraged. If new scientific data emerge that indicate that an existing biopsy or surgical specimen is suboptimal for identification of subjects, only new biopsies will be acceptable for determination of PD-L1 status. The specimen will be evaluated at a central laboratory facility for expression status of PD-L1 in a prospective manner.

The design for each of the cohorts is described below:

Part 1

Cohort A (paclitaxel and carboplatin) – First Line subjects who have any histology and who have wild type EGFR and negative ALK translocation status.

Twenty-four subjects will be randomized to treatment with MK-3475 at either 2 mg/kg or 10 mg/kg (12 subjects per dose arm) in combination with paclitaxel and carboplatin every 3 weeks (Q3W) for 4 cycles as described in the body of the protocol.

If ≤ 2 of 12 subjects at 10 mg/kg have DLT during the first cycle, the dose level is considered acceptable and will be considered the MTD. If 3 or more of the 12 subjects treated at 10 mg/kg have DLT, the 10 mg/kg dose will be considered unacceptable. If the 10 mg/kg dose has been ruled out and if ≤2 of 12 subjects at 2 mg/kg have DLT, the 2 mg/kg dose will be considered acceptable and will be considered the MTD. If 3 or more of the 12 subjects treated at 2 mg/kg have DLT, the 2 mg/kg dose will be considered unacceptable and the cohort discontinued. After completion of 4 cycles of chemotherapy subjects will continue treatment with MK-3475 until progression of disease and or unacceptable toxicity as defined in Section 5.2.1.2 up until a maximum of 35 cycles (approximately 2 years).

Cohort B (paclitaxel, carboplatin and bevacizumab) – First Line subjects who have non-squamous histology and who have wild type EGFR and negative ALK translocation status.

The design for cohort B will be the same as cohort A except that the chemotherapy will consist of paclitaxel, carboplatin and bevacizumab. In addition, subjects should receive maintenance bevacizumab at the discretion of the investigator with MK-3475 until progression or unacceptable toxicity as defined in Section 5.2.1.2 for a maximum of 35 cycles (approximately 2 years).

Cohort C (carboplatin and pemetrexed) – First Line subjects who have non-squamous histology and who have wild type EGFR and negative ALK translocation status.

The design for cohort C will be the same as cohort A, except that the chemotherapy will consist of carboplatin and pemetrexed. In addition, subjects should receive maintenance pemetrexed at the discretion of the investigator with MK-3475 until progression or unacceptable toxicity as defined in Section 5.2.1.2 for a maximum of 35 cycles (approximately 2 years).

Cohort D (ipilimumab plus MK-3475) – Subjects with any histology and have failed previous treatment. Subjects with EGFR mutations or ALK translocations must have progressed on appropriate targeted therapies (e.g., erlotinib, gefitinib, crizotinib). After starting enrollment into cohort D, additional safety information became available from the nivolumab and ipilimumab combination study in advanced NSCLC patients which raised safety concerns of the combination including treatment-related deaths [67]. Based on the data, the Sponsor has decided to decrease the dose of combination to dose level -2; Ipilimumab 1 mg/kg combined with MK-3475 2 mg/kg. At the time of the decision, a total of 6 patients (3 patients at Ipilimumab 1 mg/kg combined with MK-3475 10 mg/kg, and 3 patients at Ipilimumab 3 mg/kg combined with MK-3475 10mg/kg) had been enrolled and treated with the combination and no DLTs have been reported. The cohort will follow a 3+3 design followed by expansion up to total 12 patients at dose level -2.

- The first 3 subjects will be treated with MK-3475 2 mg/kg Q3W in combination with ipilimumab 1 mg/kg. If ≤1 DLTs occur in these 3 subjects during the first cycle (3 weeks) of treatment, 3 more subjects will be enrolled. If ≤1 DLTs occur in 6 subjects, the dose level will be declared as the RP2D and 6 additional subjects will be enrolled at the dose as an expansion cohort.
- If ≥2/3 or ≥2/6 subjects treated with MK-3475 2 mg/kg Q3W in combination with ipilimumab 1 mg/kg have a DLT, the cohort will be discontinued.

Cohort E (erlotinib plus MK-3475) – First Line subjects who have activating EGFR mutations, negative ALK translocation and any histology. Treatment will follow 3+3 design followed by cohort expansion with MK-3475 2 mg/kg Q3W in combination with erlotinib daily. A total of 12 subjects will be treated.

The first 3 subjects will be treated with MK-3475 2 mg/kg Q3W in combination with erlotinib daily as described in the body of the protocol. If ≤1 DLTs occur in these 3 subjects during the first cycle (3 weeks) of treatment, the next 3 subjects will be treated. If ≤1 of the 6 subjects have a DLT, the dose level is considered acceptable for phase II. If ≥2/3 or ≥2/6 subjects treated have a DLT, the combination will be defined as unacceptable and the cohort will be discontinued. Missing >10% of erlotinib dose in the first cycle for any reason other than study drug-related toxicity will be considered noncompliance and the subject will be replaced. Erlotinib will be continued as long as the subject is receiving benefits whereas MK-3475 will be limited to a maximum of 35 cycles (approximately 2 years).

Cohort F (gefitinib plus MK-3475) – First Line subjects who have activating EGFR mutations, negative ALK translocation and any histology. Treatment will follow 3+3 design followed by cohort expansion with MK-3475 2 mg/kg Q3W in combination with gefitinib. A total of 12 subjects will be treated. The first 3 subjects will be treated with MK-3475 2 mg/kg Q3W in combination with gefitinib daily as described in the body of the protocol. If ≤1 DLTs occur in these 3 subjects during the first cycle (3 weeks) of treatment, the next 3 subjects will be treated. If ≤1 of the 6 subjects have a DLT, the dose level is considered acceptable for phase II. If ≥2/3 or ≥2/6 subjects treated have a DLT, the institution of a dose separation phase will be initiated as described below. Missing >10% of gefitinib dose during the first cycle for any reason other than study drug-related toxicity will be considered noncompliance and the subject will be replaced. Gefitinib will be continued as long as the subject is receiving benefits whereas MK-3475 will be limited to a maximum of 35 cycles (approximately 2 years).

If the dose combination in Cohort F as described above results in a high level of discontinuations at Cycle 2 or 3 the Dose Separation Phase may be initiated even though the combination was found to be tolerable as defined by the DLT rules above.

Cohort F Dose Separation Phase (gefitinib plus MK-3475) - Treatment will follow 3+3 design followed by cohort expansion with gefitinib daily for the first 6 weeks of treatment followed by MK-3475 2 mg/kg Q3W in combination with gefitinib daily. A total of 12 subjects will be treated.

The first 3 subjects will be treated with gefitinib daily for the first 6 weeks of treatment followed by MK-3475 2 mg/kg Q3W in combination with gefitinib daily as described in the body of the protocol. If drug-related toxicities ≥ Grade 3 occur during the first 6 weeks of gefitinib monotherapy the patient should be discontinued from the treatment phase and not receive gefitinib and MK-3475 combination at Cycle 1. If ≤ 1 DLTs occur in these 3 subjects during Cycle 1 and 2 (Weeks 7 – 12) of treatment, the next 3 subjects will be treated. If ≤1 of the 6 subjects have a DLT, the dose level is considered acceptable for phase II. If ≥2/3 or ≥2/6 subjects treated have a DLT, the combination will be defined as unacceptable and the cohort will be discontinued. Missing >10% of gefitinib dose in the first 9 weeks for any reason other than study drug-related toxicity will be considered noncompliance and the subject will be replaced. Gefitinib will be continued as long as the subject is receiving benefits whereas MK-3475 will be limited to 35 cycles (approximately 2 years).

Part 2

Cohorts G1 and G2 – First Line subjects who are EGFR wild type non-squamous histology.

Subjects will be screened for the presence of PD-L1 expression, ALK translocation and EGFR mutation. Subjects who are EGFR wild type and do not have ALK translocation and otherwise eligible for randomization will be enrolled in cohort G1. Subjects with non-squamous histology will be randomized to receive carboplatin and pemetrexed alone for 4 cycles followed by maintenance pemetrexed at the discretion of the investigator until progression or unacceptable toxicity as defined in Section 5.2.1.2 or carboplatin and pemetrexed plus MK-3475 200mg for 4 cycles followed by maintenance pemetrexed with MK-3475 at the discretion of the investigator until progression or unacceptable toxicity as defined in Section 5.2.1.2. MK-3475 is limited to a maximum of 35 treatment cycles. Treatment with maintenance pemetrexed does not have a maximum duration and may continue within local regulations and the investigator's judgment until reaching a protocol-specified discontinuation criterion (eg, progressive disease, toxicity, withdrawal of consent, physician decision, end of study). Subjects assigned to the chemotherapy arm will have the opportunity to crossover to receive MK-3475 monotherapy once they experience progression of disease (PD) defined by RECIST 1.1 and meet all crossover criteria defined in Section 7.1.5.5. Treatment is limited up to 17 cycles for patients who crossover to MK-3475 monotherapy. The Sponsor may elect to add additional arm(s) (treatment from Cohort A (paclitaxel and carboplatin), or treatment from Cohort B (paclitaxel, carboplatin and bevacizumab)) to cohort G1 based on additional data available from Part 1 of the study.

Cohort G2 will be optional and dependent upon results of G1. If Cohort G1 does not achieve the prespecified target HR, but an analysis suggests a strong correlation between PD-L1 expression levels and anti-tumor activity then Cohort G2 will initiate with a biomarker-selected population. Cohort G2 will randomize 60 subjects to receive either carboplatin and pemetrexed alone for 4 cycles followed by maintenance pemetrexed at the discretion of the investigator until progression or unacceptable toxicity as defined in Section 5.2.1.2 or carboplatin and pemetrexed plus MK-3475 200mg for 4 cycles followed by maintenance pemetrexed with MK-3475 at the discretion of the investigator until progression or unacceptable toxicity as defined in Section 5.2.1.2 for a maximum of 35 cycles

(approximately 2 years). Subjects assigned to the chemotherapy arm will have the opportunity to crossover to receive MK-3475 monotherapy once they experience progression of disease (PD) defined by RECIST 1.1 and meet all crossover criteria defined in Section 7.1.5.5. Treatment is limited up to 35 cycles for the patients who crossover to MK-3475 monotherapy.

Note that subjects receiving chemotherapy only in cohort G will have a slightly modified laboratory assessment follow-up. See Section 6.1 for details.

Cohort H (ipilimumab plus MK-3475) – Subjects with any histology and have failed prior treatments. Subjects with EGFR mutations or ALK translocations must have progressed on appropriate targeted therapies (e.g., erlotinib, gefitinib, crizotinib)

Subjects assigned to cohort H will receive ipilimumab at the RP2D from Part 1, cohort D for 4 cycles in combination with MK-3475 followed by MK-3475 monotherapy.

2.1.1 Definition of Dose-Limiting Toxicities

All toxicities will be graded using National Cancer Institute (NCI) CTCAE Version 4.0 (Appendix 12.6).

The DLT window of observation will be one cycle.

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

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

2. Grade 4 hematologic toxicity lasting ≥7 days.

3. Grade 3 non-hematologic toxicity (not laboratory, specifically nausea, vomiting and diarrhea) lasting >3 days despite optimal supportive care.

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

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

5. Febrile neutropenia Grade 3 or Grade 4:

   - Grade 3 is defined as ANC <1000/mm^3 with a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of ≥38 degrees C (100.4 degrees F) for more than one hour

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

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

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

7. Prolonged delay (>2 weeks) in initiating Cycle 2 due to treatment-related toxicity

8. Missing >10% of erlotinib or gefitinib doses as a result of AE(s) during the DLT window of observation.

9. Grade 5 toxicity.

2.1.2 Replacement of Subjects in DLT Observation Period

Subjects who received < 90% of the MK-3475 infusion during the DLT window of observation as defined in 2.1.1 (e.g., because the infusion had to be discontinued due to an infusion reaction) and did not experience a DLT will not be taken into account in the assessment of the overall DLT rate for the particular dose level cohort and need to be replaced.

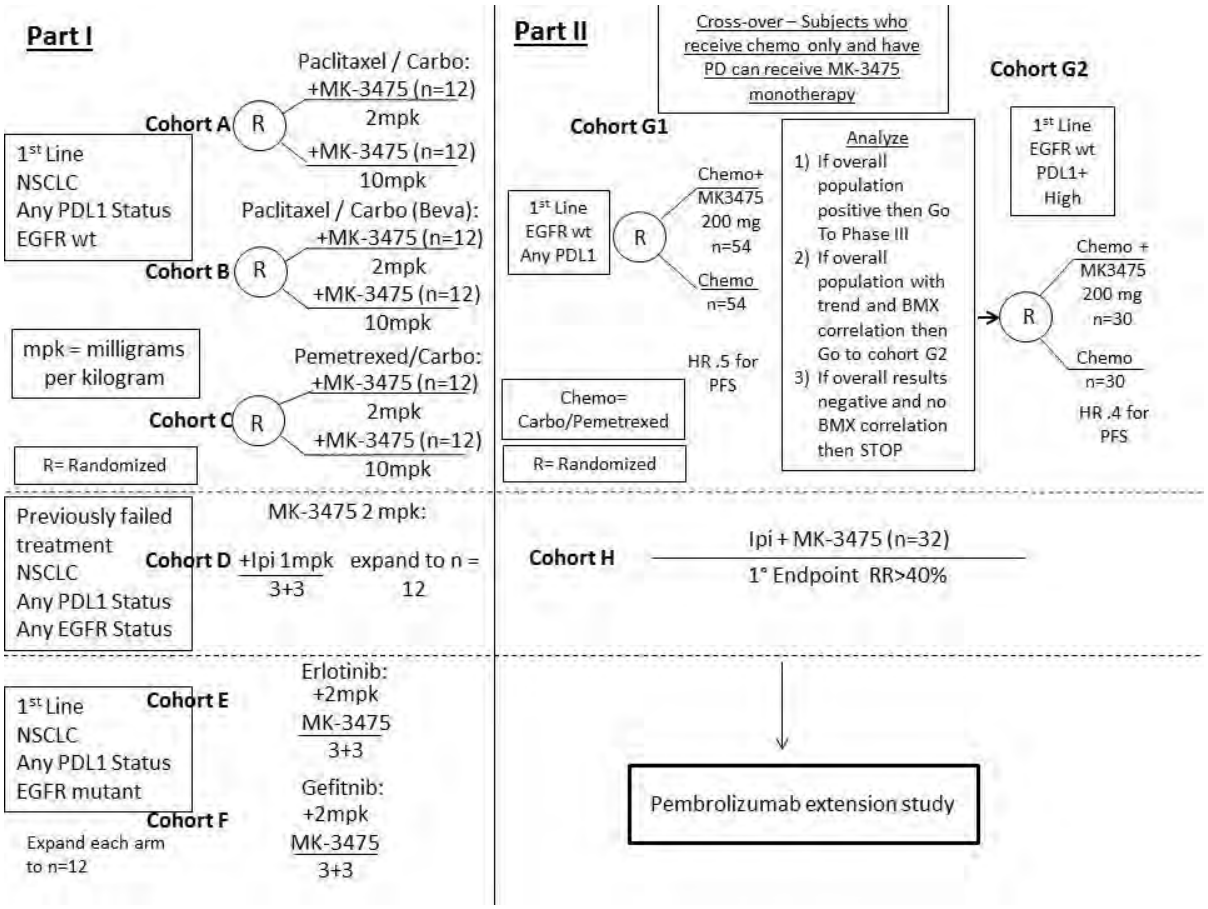
If a subject experiences a DLT during the DLT window of observation as defined in 2.1.1, study therapy may be discontinued following discussion and agreement between the Sponsor and investigator. An alternative consideration may be dose modification of MK-3475 as described in Section 5.2.1.2 with continued therapy.

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

2.2 Trial Diagram

The trial design is depicted in Figure 1 below.

Figure 1 Trial Design



3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

3.1 Primary Objective(s) & Hypothesis(es)

1) **Primary Objective Part 1:** To determine the recommended Phase II dose for MK-3475 in combination with chemotherapy or immunotherapy in subjects with unresectable or metastatic NSCLC.

2) **Primary Objective Part 2:** To evaluate anti-tumor activity based on RECIST 1.1 of MK-3475 in combination with chemotherapy or immunotherapy in NSCLC subjects using objective response rate (ORR).

Hypotheses:

- Cohort G1: MK-3475 in combination with chemotherapy improves ORR per RECIST 1.1 by blinded independent central review in NSCLC subjects compared to chemotherapy alone.

- Cohort H: MK-3475 in combination with immunotherapy results in an ORR of greater than 20% per RECIST 1.1 by blinded independent central review in NSCLC subjects.

3.2 Secondary Objective(s) & Hypothesis(es)

1) **Objective**: To evaluate anti-tumor activity based on RECIST 1.1 of MK-3475 in combination with chemotherapy in NSCLC subjects using progression-free survival (PFS).

   Cohort G1 Hypothesis: MK-3475 in combination with chemotherapy prolongs PFS per RECIST 1.1 by blinded independent central review in NSCLC subjects compared to chemotherapy alone treatment.

2) **Objective**: To evaluate duration of response (DOR) per RECIST 1.1 by blinded independent central review in subjects with unresectable or metastatic NSCLC treated with MK-3475 in combination with chemotherapy or immunotherapy or chemotherapy alone.

3) **Objective**: To evaluate the overall survival (OS) in subjects with unresectable or metastatic NSCLC treated with MK-3475 in combination with chemotherapy or immunotherapy or chemotherapy alone.

4) **Objective:** To characterize the pharmacokinetic (PK) profile of MK-3475 when given in combination with chemotherapy or ipilimumab or TKI (gefitinib or erlotinib).

5) **Objective**: To evaluate anti-tumor activity based on modified RECIST 1.1 of MK-3475 in combination with chemotherapy or immunotherapy or TKI (Part 1).

6) **Objective:** To evaluate the correlation between PD-L1 expression levels and anti-tumor activity of MK-3475 in cohort G1.

3.3 Exploratory Objectives

1) To evaluate PFS and OS following crossover to MK-3475 in subjects treated with chemotherapy alone until disease progression.

2) To explore the correlation of tumor measurements (e.g., single longest diameter or volume) with PFS and OS in previously treated subjects with NSCLC in subjects receiving MK-3475 in combination with chemotherapy versus chemotherapy alone.

3) To investigate other biomarkers that may correlate with tumor response.

4.0 BACKGROUND & RATIONALE

4.1 Background

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

4.1.1 Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades [1]. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies [2-37]. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells / FoxP3+ regulatory T-cells seems to correlate with improved prognosis and long-term survival in solid malignancies such as ovarian, colorectal and pancreatic cancer, hepatocellular carcinoma, malignant melanoma (MEL) and renal cell carcinoma (RCC). TILs can be expanded ex vivo and re-infused, inducing durable objective tumor responses in cancers such as MEL [38, 39].

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an Ig superfamily member related to CD28 and CTLA-4 which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) [40; 41]. The mechanism by which PD-1 down modulates T-cell responses is similar to, but distinct from that of CTLA-4 as both molecules regulate an overlapping set of signaling proteins [42; 34]. PD-1 was shown to be expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B-cells, T regs and Natural Killer cells [43; 44]. The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types, including non-hematopoietic tissues as well as in various tumors [42; 45-47]. Both ligands are type I transmembrane receptors containing both IgV- and IgC-like domains in the extracellular region and contain short cytoplasmic regions with no known signaling motifs. Binding of either PD-1 ligand to PD-1 inhibits T-cell activation triggered

through the T-cell receptor. PD-L1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments. PD-L2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T-cell function in peripheral tissues [45]. 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 [48], pancreatic carcinoma [49], hepatocellular carcinoma [50], and ovarian carcinoma [51]. Furthermore, PD-1 has been suggested to regulate tumor-specific T-cell expansion in subjects with MEL [52].

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.

Anti-mouse PD-1 or anti-mouse PD-L1 antibodies have demonstrated anti-tumor responses as a monotherapy in models of squamous cell carcinoma, pancreatic carcinoma, MEL and colorectal carcinoma. Blockade of the PD-1 pathway effectively promoted CD8+ T-cell infiltration into the tumor and the presence of IFN-γ, granzyme B and perforin, indicating that the mechanism of action involved local infiltration and activation of effector T-cell function in vivo [51; 53-57]. In addition, the combination of gemcitabine and anti-PD-L1 mAb demonstrated synergy in the rejection of pancreatic mouse tumors [49]. In-house experiments have confirmed the in vivo efficacy of PD-1 blockade as a monotherapy as well as in combination with chemotherapy in syngeneic mouse tumor models (see the IB).

Recent data of nivolumab (MDX-1106, BMS-936558), an IgG4 antibody against PD-1, have validated PD-1 as an attractive target for clinical therapeutic intervention in NSCLC subjects [18; 59]. Nivolumab was tested in multiple solid tumors in an open-label Phase I trial and promising clinical activity was noted in subjects with MEL, RCC, and NSCLC at multiple doses. After an initial cohort of subjects with previously treated NSCLC were treated at 10 mg/kg every 2 weeks (Q2W) with nivolumab, the study permitted randomization among 3 dose levels for new subjects in this population 1, 3, and 10 mg/kg Q2W. Overall, subjects with progressive NSCLC from prior therapies who were exposed to nivolumab had a 16% (20/122) ORR [59]. Those treated with nivolumab at 1 mg/kg administered every 2 weeks (Q2W) had only a 3% (1/31) ORR with a response lasting greater than 11 months. Those treated with nivolumab at 3 mg/kg Q2W had a 27% (9/33) ORR with one responder having a response of greater than 30 months. Those treated at 10 mg/kg Q2W had a 17% (10/58) ORR, with one response lasting greater than 18 months. The most common drug-related adverse events (AEs), occurring in 5% or more of previously treated subjects with NSCLC, included decreased appetite, decreased hemoglobin, diarrhea, nausea, pruritus, fatigue, and rash. The most commonly observed Gr 3-4 drug-related AEs in previously treated subjects with NSCLC were elevated aspartate aminotransferase (AST), fatigue, and pneumonitis [58]. Of note, 3 deaths involving pneumonitis were observed on this trial, 2 of these subjects were receiving anti-PD-1 therapy for NSCLC [18].

4.1.2 Preclinical and Clinical Trials

An open-label Phase I trial (Keynote 001) is being conducted to evaluate the safety and clinical activity of single agent pembrolizumab. The dose escalation portion of this trial evaluated 3 dose levels, 1 mg/kg, 3 mg/kg, and 10 mg/kg, administered every 2 weeks (Q2W), in subjects with advanced solid tumors. All 3 dose levels were well tolerated and no dose - limiting toxicities were observed. Based on pharmacokinetic (PK) data showing a half-life of 21 days, the protocol was amended to change the dosing frequency in the expansion cohort to Q3W. The ongoing expansion cohort in Keynote 001 is enrolling subjects with NSCLC.

Keynote 001, Part C enrolled 38 subjects with NSCLC (adenocarcinoma, squamous cell carcinoma, and large cell carcinoma) who experienced progression of cancer after initiation of their second line of systemic therapy to receive monotherapy pembrolizumab. By investigator-assessed irRC (immune-related response criteria), the ORR (confirmed and unconfirmed) was 24%. Similar results were obtained using RECIST 1.1, yielding an ORR (confirmed and unconfirmed) of 21%. Most responses by irRC were observed by the time of first planned assessment at Week 9. The median duration of response by irRC has not been reached with a median duration of follow-up of 62 weeks. The median OS for all 38 patients treated with pembrolizumab was 51 weeks.

Subjects were required to submit a newly obtained tumor biopsy prior to initiating therapy with pembrolizumab to evaluate for expression of PD-L1, the presumptive predictive biomarker of pembrolizumab, using a preliminary immunohistochemistry assay. A modified H-score scoring system of PD-L1 expression was established for NSCLC by analyzing tumor specimens from resected NSCLC specimens. This scoring system was then applied to the samples from Keynote 001, Part C.

A total of 35 patients from Keynote 001 had tumor samples evaluable and a clinical response assessed. All but 3 patients were from Part C; 3 patients from Part A had NSCLC, submitted tumor tissue, and had a clinical response assessment. Seven of the 35 patients had a clinical response (20%) by investigator assessed irRC. Six responders (26%) were observed among the 23 patients whose tumors expressed PD-L1. Of note, these 6 responders clustered at the higher end of the modified H-score. Six of 9 (67%) patients whose tumors expressed PD-L1 to an extent above the preliminary cut point had a clinical response. No responses were noted among the patients whose tumors did not express PD-L1.

Keynote 001 Part F is currently enrolling PD-L1 positive previously untreated subjects with advanced NSCLC (Part F1) or previously treated subjected with advanced NSCLC (Part F2).

The planned enrollment for Part F1 is ~88 subjects; preliminary data from 45 subjects indicates an ORR by investigator assessed irRC of 36%. Median OS at 12 months has not been reached with an OS rate at 12 months of 79.7%. For the subjects enrolled onto Part F2, the median PFS by investigator assessed irRC was 26.4 weeks in the highest PD-L1 positive cohort (PD-L1 “strong”); the median OS in the same cohort was 13.7 months.

A training set comprised of approximately 140 tumor samples and their associated clinical outcome data were used to assess an optimal cut point for PD-L1 positivity. An optimal PD-L1 cut point was identified by receiver operator characteristic curve analyses and by considering clinical implications of false positive and false negative results. Cut points were identified based upon a proportions score (PS) method of IHC analysis with the tumors expressing at or greater than the highest cut point (PS ≥50%) referred to as PD-L1 strongly positive tumors, and tumors expressing ≥1% but less than 50% referred to as the PD-L1 weak tumors. Outcomes based on irRC were used as the primary outcome for the analysis. Based on the training set, the Positive Predictive Value for patients in the strong category was 42% while maintaining a negative predictive value of 92% for patients in the weak or null category. Given the limited activity in the PD-L1 negative population, they will be excluded from the study. Furthermore, preliminary data indicate that the prevalence of PD-L1 positivity in the previously untreated, Keynote 001, Part F1 cohort is approximately 78%.

4.1.2.1 Preclinical Background on Combinations

MK-3475 relies upon a functional immune system to exert its anti-tumor effect, as previously discussed. Theoretically, an even greater tumor cell reduction might be achieved by enhancing the antigen presentation via administration of MK-3475 in combination with standard cytotoxic chemotherapy. Provided the cytotoxic chemotherapy combination is not also immunosuppressive, this coadministration should show increased anti-tumor activity. Indeed Figures 9-12 of the IB describe syngeneic colon cancer murine models that demonstrate this very principle. Mice receiving the anti-PD-1 mAb plus 5-FU or gemcitabine experienced a greater tumor volume reduction and survival. So it is reasonable to explore such effects in humans, but first a safe dose must be identified.

4.1.3 Information on Other Trial-Related Therapy

Current standard in a first line setting for advanced NSCLC except EGFR mutated type and EML4-ALK is platinum-based doublet therapy. While platinum doublets have similar outcomes [59; 60], cisplatin/pemetrexed or carboplatin/paclitaxel have been clinically widely used mainly on the basis of safety. Median survival was 10.3 months of NSCLC subjects who were treated with cisplatin/pemetrexed in a first line setting. Frequent (>5%) Grade 3 or 4 drug-related toxicities were neutropenia, anemia, nausea, vomiting, and fatigue [59]. The median survival was 12.3 months for NSCLC subjects who were treated with carboplatin/paclitaxel in a first line setting. Frequent (>5%) Grade 3 or 4 toxicities were leukopenia, neutropenia, anemia, thrombocytopenia, febrile neutropenia, nausea, vomiting, anorexia and constipation [61]. The addition of bevacizumab to carboplatin/paclitaxel followed by bevacizumab maintenance therapy in subjects who are eligible for treatment has been demonstrated in improved overall survival [62]. Despite the responses observed in NSCLC subjects with chemotherapy, almost all subjects eventually progress and die as a consequence of their NSCLC.

For subjects with EGFR mutations, treatment with erlotinib or gefitinib is the standard of care as monotherapy. Despite response rates in excess of 50%, and improved overall survival, almost all subjects eventually progress and need additional treatment options.

Therefore, new therapies are necessary for the treatment of subjects with advanced or metastatic NSCLC.

Nivolumab has been evaluated in combination with chemotherapy in subjects with NSCLC. The preliminary data are summarized below:

Nivolumab has been studied in combination with chemotherapy in subjects with NSCLC [63]. The study enrolled first line NSCLC patients regardless of PD-L1 status. The study explored nivolumab 10 mg/kg Q3W (except one arm at 5 mg/kg as noted below) in combination with 3 standard chemotherapy regimens. The chemotherapy was given for 4 cycles concurrently with nivolumab followed by nivolumab monotherapy. The preliminary results are shown below:

	Nivo 10 + gem/cis Sq	Nivo 10 + pem/cis Non-sq	Nivo 10 + pac/carb Sq + Non-sq	Nivo 5 + pac/carb Sq + Non-sq
N	12	15	15	14
ORR, [a] n (%)	4 (33)	7 (47)	7 (47)	7 (50)
Median duration of response (Kaplan-Meier),[a] wk (range)	20.9 (12.1–41.7+)	32.0 (13.1–42.1+)	25.6 (11.4+–39.0+)	Not reached (11.4–37.3+)
PD as BOR, n (%)	0	0	3 (20)	1 (7)
PFS rate wk 24, %	36	71	38	57
1-yr OS, %	59	87	59	Insufficient follow-up

[a] Confirmed responses only. + Ongoing.

The data indicate that the combination of an anti-PD-1 therapy in combination with chemotherapy has demonstrated encouraging response rates and as well as 1 year OS rates; however, 45% of the patients in the study experienced treatment-related Grade 3 or 4 AEs. Therefore, randomized phase II data with the combination will be necessary to determine the relative improvement in benefit/risk compared to chemotherapy alone.

Given the potential limitations of combinations with chemotherapy, another approach is the addition of anti-PD-1 to ipilimumab. The rationale is that blocking of PD-1 receptors and CTLA4 receptors results in T-lymphocytes being fully disinhibited. Preclinical studies have demonstrated synergy between nivolumab and ipilimumab [64] and a clinical trial in first line patients with advanced NSCLC has shown anti-tumor activity when combining these 2 treatments. However, increased toxicities were seen from the combination including treatment-related deaths (N=3 [7%]) and discontinuation due to AEs (N=16 [35%]) [67]. The preliminary efficacy data are shown below:

	N1 + I3 Sq	N1 + I3 Non-sq	N3 + I1 Sq	N3 + I1 Non-sq
N	7	15	8	16
ORR,[a] n (%)	1 (14)	1 (7)	2 (25)	2 (13)
ORR,[b] n (%)	1 (14)	2 (13)	3 (38)	4 (25)
	3 (14)		7 (29)	
SD, n (%)	2 (29)	6 (40)	4 (50)	3 (19)
mDOR (Kaplan-Meier),[a] wk (range)	NR (9+)	NR (21+)	17 (12, 21)	NR (24+, 25+)
Ongoing responders,[a] n (%)	1 (100)	1 (100)	0	2 (100)

[a] Confirmed OR only. [b] Confirmed + unconfirmed OR.

Furthermore, ipilimumab has demonstrated activity in NSCLC in combination with chemotherapy [65].

Therefore, combination immunotherapy offers a potential advantage that warrants further exploration in NSCLC patients who do not have other effective treatment options.

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

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.

Lung cancer has been the most common malignancy in the world for several decades and it also has been the leading cause of cancer related mortality. In 2008, there were more than 1.6 million newly diagnosed lung cancer cases and 1.4 million cases of lung cancer related deaths worldwide.

Despite the recent progress in lung cancer treatment, overall survival for advanced NSCLC remains short and almost all patients die within 1 year from the initial diagnosis. Advanced lung cancer subjects without EGFR mutation or EML4-ALK translocation are often treated with platinum-based combination chemotherapy with or without bevacizumab. Overall response rates and PFS from these first line regimens range 15-35% and 4-6 months respectively. For patients with EGFR mutations or EML4-ALK translocations, the development of targeted therapies has improved clinical outcomes; however, overall survival remains poor with a median less than 2 years. Therapy for patients with this stage of disease

is not curative, and disease progression is expected. Therefore, new therapies are needed for patients with advanced or metastatic NSCLC.

Anti-tumor activity of MK-3475 is being tested in NSCLC patients in MK-3475 PN001 and preliminary data revealed encouraging response rates. Moreover, when MK-3475 was administered in combination with other chemotherapeutic agents in mouse models, synergistic anti-tumor effects were observed (refer to the IB, Section 4.1.6 and 4.1.7). Therefore, clinical development of MK-3475, an anti-PD-1 antibody, in combination with chemotherapy would potentially have a great significance in patients with advanced solid tumors including NSCLC.

4.2.2 Rationale for Dose Selection/Regimen

In general, the dose and schedule for MK-3475 used in the study is based on the results of PN001. (See IB.)

Cohorts A, B and C – The chemotherapy regimens are either the approved dose and schedule for each regimen or a standard modification of the regimen [62; 66]. In the phase I study, no DLTs were seen within the first 4 weeks of treatment when nivolumab was given at 10 mg/kg Q3W in combination with chemotherapy as mentioned above [63]. Therefore, a randomized phase I design will be employed to evaluate MK-3475 at doses of 2 mg/kg vs. 10 mg/kg for 12 subjects.

Cohort D - When tested in advanced melanoma patients, ipilimumab at 3 mg/kg in combination with nivolumab 1 mg/kg every 3-week schedule demonstrated an acceptable safety profile. However, after starting enrollment into cohort D, additional safety information became available from the nivolumab and ipilimumab combination study in advanced NSCLC patients which raised safety concerns of the combination including treatment-related deaths [67], the Sponsor has decided to decrease the dose of combination to dose level -2; Ipilimumab 1mg/kg combined with MK-3475 2mg/kg. At the time of the decision, a total of 6 patients (3 patients at Ipilimumab 1mg/kg combined with MK-3475 10mg/kg, and 3 patients at Ipilimumab 3mg/kg combined with MK-3475 10mg/kg) had been enrolled and treated with the combination in Cohort D and no DLTs have been reported.

Cohort E and F – Treatment will consist of MK-3475 2 mg/kg Q3W in combination with standard doses of gefitinib or erlotinib. The MK-3475 dose will follow a 3+3 dose escalation schema.

Cohort G1 - The rationale for further exploration of lower doses of MK-3475 in solid tumors is based on: 1) similar efficacy and safety of MK-3475 when dosed at either 2 mg/kg, 10 mg/kg Q3W, or 10 mg/kg Q2W in melanoma patients, 2) the flat exposure -response relationships of MK-3475 for both efficacy and safety in the dose ranges of 2 mg/kg Q3W to 10 mg/kg Q3W, 3) the lack of effect of tumor burden or indication on distribution behavior of MK-3475 (as assessed by the population PK model) and 4) the assumption that the dynamics of PD-1 target engagement will not vary meaningfully with tumor type.

The choice of the 200 mg Q3W as an appropriate dose for the switch to fixed dosing is based on simulations performed using the population PK model of MK-3475 showing that the fixed dose of 200 mg every 3 weeks will provide exposures that 1) are optimally consistent with those obtained with the 2 mg/kg dose every 3 weeks, 2) will maintain individual patient exposures in the exposure range established in melanoma as associated with maximal efficacy response and 3) will maintain individual patients exposure in the exposure range established in melanoma that are well tolerated and safe.

4.2.2.1 Starting Dose for This Trial

The starting dose for MK-3475 in this trial is 2 or 10 mg/kg Q3W.

4.2.2.2 Maximum Dose/Exposure for This Trial

The maximum dose and exposure of MK-3475 allowed in this study is 10 mg/kg Q3W up to 35 cycles (approximately 2 years). If a subject completes 35 cycles and later experiences PD, he/she may be eligible to receive up to 17 additional cycles (approximately 1 year) of MK-3475 200mg Q3W, termed Second Course (see Section 7.1.5.4).

4.2.2.3 Rationale for Dose Interval and Trial Design

Please see Section 4.2.2 for the rationale for dose interval and trial design.

4.2.3 Rationale for Endpoints

4.2.3.1 Efficacy Endpoints

The anti-tumor activity will be evaluated as an efficacy endpoint based on radiographic (CT or MRI). RECIST 1.1 (Section 12.7) will be applied for evaluation of tumor response. For the purposes of this study, RECIST 1.1 is modified to include a confirmatory scan for disease progression. This modification was a result of regulatory agency feedback and was prompted by the clinical observation that some subjects can have a temporary increase in existing tumor lesions or the transient occurrence of a new lesion after start of immunotherapy, while ultimately experiencing treatment benefit in form of an objective disease response or long-lasting disease stabilization.

4.2.3.2 Safety Endpoints

The safety primary endpoint in this study is the incidence of DLTs observed in the DLT evaluation period. Adverse events and laboratory test values observed in this study are also safety endpoints. In addition to general laboratory tests, immune laboratory tests will be evaluated considering the mode of action of MK-3475.

4.2.3.3 Pharmacokinetic Endpoints

Pharmacokinetic endpoints will include MK-3475 levels as well as anti-drug antibodies.

Pharmacokinetics of pembrolizumab will be explored per existing modeling analysis plan (MAP).

4.2.3.4 Planned Exploratory Biomarker Research

PD-L1 is a ligand for PD-1 and MK-3475 attempts to disrupt the interaction of 2 proteins. 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, pancreatic carcinoma, hepatocellular carcinoma, ovarian carcinoma, and NSCLC.

The correlation between baseline PD-L1 expression levels and tumor response will be evaluated as an exploratory objective. PD-L1 expression levels will be measured in archival tumors or biopsy samples determined to be evaluable by central lab.

4.2.3.5 Future Biomedical Research

Merck will conduct Future Biomedical Research on DNA (blood) or 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. Specimens may be used for future assay development.

Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol (as part of the main trial) and will only be conducted on specimens from appropriately-consented subjects. The objective of collecting specimens for Future Biomedical Research is to explore and identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments. For instance, exploratory pharmacogenetic (PGt) studies may be performed if significant Pharmacokinetic/Pharmacodynamic (PK/PD) relationships are observed or adverse events are identified. Genomic markers of disease may also be investigated. Such retrospective pharmacogenetic studies will be conducted with appropriate biostatistical design and analysis and compared to PK/PD results or clinical outcomes. Any significant PGt relationships to outcome would require validation in future clinical trials. The overarching goal is to use such information to develop safer, more effective drugs/vaccines, and/or to ensure that subjects receive the correct dose of the correct drug/vaccine at the correct time. The details of Future Biomedical Research 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 ≥ 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) Have a histologically-confirmed or cytologically confirmed diagnosis of stage IIIB/IV NSCLC

    a. Subjects for cohort A, B, C, E, F and G should have received no prior systemic treatment for stage IIIb/IV NSCLC.

    b. Subjects for cohorts D and H should have received prior treatment for NSCLC which should have been platinum based, unless EGFR mutation or ALK translocation was present. Subjects who are eligible for specific targeted therapy (e.g., EGFR mutation or ALK translocation) should have received prior treatment with the appropriate targeted agents.

    c. Subjects for cohorts E and F should have confirmed activating EGFR mutation.

2) Patients who had disease progression >1yr after completing adjuvant therapy for stage I-IIIA disease are eligible for Cohort A, B, C, G1 and G2, as long as no systemic therapy was given for the recurrent disease.

3) Subject must have at least one radiographically measurable lesion as per RECIST 1.1 defined as a lesion that is ≥10 mm in longest diameter or lymph node that is ≥15 mm in short axis imaged by CT scan or MRI

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

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

6) Have a performance status of 0 or 1 on the Eastern Cooperative Oncology Group (ECOG) Performance Status (Section 12.4)

7) 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.

8) Have adequate organ function as indicated by the following laboratory values:

Table 1 Adequate Organ Function Lab 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– 4 weeks without transfusions
Renal	
Serum 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	
Serum 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 will still be eligible if total T3 or free T3 and free T4 are within the normal limits.

9) Female subjects of childbearing potential must have a negative urine or serum pregnancy test within 72 hours prior to receiving the first dose of study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

10) Female subjects of childbearing potential (Section 5.7.2) must be willing to use an adequate method of contraception as outlined in Section 5.7.2 – Contraception, for the course of the study through 120 days after the last dose of study medication and up to 180 days after last dose of chemotherapeutic agents or TKIs.

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

11) Male subjects of childbearing potential (Section 5.7.2) must agree to use an adequate method of contraception as outlined in Section 5.7.2- Contraception, starting with the first dose of study therapy through 120 days after the last dose of study therapy and up to 180 days after last dose of chemotherapeutic agents or TKIs.

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

12) Subject has voluntarily agreed to participate by giving written informed consent/assent for the trial. The 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) Is currently participating and receiving study therapy or has participated in a study of an investigational agent and received study therapy or used an investigational device within 4 weeks prior to administration of MK-3475.

2) a) Within 3 weeks of the first dose of trial treatment:

- Has received prior systemic cytotoxic chemotherapy
- Has received antineoplastic biological therapy (e.g., cetuximab)
- Had major surgery

b) Received radiation therapy to the lung that is > 30 Gy within 6 months of the first dose of trial treatment

c) Received prior tyrosine kinase inhibitor therapy or completed

palliative radiotherapy within 7 days of the first dose of trial treatment.

3) Is expected to require any other form of antineoplastic therapy while on study.

4) Has received a live-virus vaccination within 30 days of planned treatment start. Seasonal flu vaccines that do not contain live virus are permitted.

5) Patients with clinically active diverticulitis, intra-abdominal abscess, GI obstruction, abdominal carcinomatosis.

6) 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 the study. 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, in situ cervical cancer, or other in situ cancers.

7) Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are clinically stable for at least 4 weeks and, have no evidence of new or enlarging brain metastases and also are off steroids 3 days prior to dosing with study medication. Stable brain metastases by this definition should be established prior to the first dose of study medication.

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

9) Has active autoimmune disease that has required systemic treatment in past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (eg., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.

10) Subjects with asthma that require intermittent use of bronchodilators, inhaled steroids, or local steroid injections would not be excluded from the study. Subjects on chronic systemic steroids would be excluded from the study.

11) Had prior treatment with any other anti-PD-1, or PD-L1 or PD-L2 agent or an antibody targeting other immuno-regulatory receptors or mechanisms. Has participated in any other MK-3475 trial and has been treated with MK-3475.

    Examples of such antibodies include (but are not limited to) antibodies against IDO, PD-L1, IL-2R, GITR.

12) Has an active infection requiring therapy.

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

14) 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.

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

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

17) 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).

18) Has symptomatic ascites or pleural effusion. A subject who is clinically stable following treatment for these conditions (including therapeutic thoraco- or paracentesis) is eligible.

19) 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.

20) Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the study.

21) Subjects in cohorts E and F 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.

22) Is or has an immediate family member (spouse or children) who is investigational site or sponsor staff directly involved with this trial, unless prospective IRB approval (by chair or designee) is given allowing exception to this criterion for a specific subject.

5.2 Trial Treatment(s)

Trial treatment should begin on the day of randomization or as close as possible to the date on which treatment is allocated/assigned. The treatments to be used in this trial are outlined below in Table 2 and in Section 5.2.2.

Table 2 Trial Treatment

Drug	Dose/ Potency	Dose Frequency	Route of Administration	Regimen/ Treatment Period	Use
Paclitaxel	200 or 175 mg/m^2	Q3W	IV infusion	Day 1 of each cycle	Treatment of cancer
Carboplatin	6 mg/ml/min (Cohorts A&B) Target AUC 5 mg/mL/min (Cohort C and G)	Q3W	IV infusion	Day 1 of each cycle	Treatment of cancer
Bevacizumab	15 mg/kg	Q3W	IV infusion	Day 1 of each cycle	Treatment of cancer
Pemetrexed	500 mg/m^2	Q3W	IV infusion	Day 1 of each cycle	Treatment of cancer

Drug	Dose/ Potency	Dose Frequency	Route of Administration	Regimen/ Treatment Period	Use
Ipilimumab	1 mg/kg	Q3W	IV infusion	Day 1 of each cycle	Experimental
Erlotinib	150 mg	Daily	PO	Daily	Treatment of cancer
Gefitinib	250 mg	Daily	PO	Daily	Treatment of cancer
MK-3475[1]	2 or 10 mg/kg	Q3W	IV infusion	Day 1 of each cycle[1,]	Experimental
MK-3475[1]	200 mg	Q3W	IV infusion	Day 1 of each cycle[1]	Experimental
[1]MK-3475 to be administered prior to chemo-/immunotherapy.					

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

5.2.1 Dose Selection/Modification

5.2.1.1 Dose Selection

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) for Part 1 of the study and Cohort H in Part 2. For Part 2, Cohort G, the dose amount required to prepare the MK-3475 infusion solution will be based on a fixed dose of 200mg. Details on the dose calculation, preparation and administration are provided in the Pharmacy Manual.

Concomitant chemotherapeutic/immunotherapeutic agents will be prepared and administered as per the approved product label.

5.2.1.2 Dose Modification (Escalation/Titration/Other)

5.2.1.2.1 Concomitant Chemotherapeutic Agents

Refer to approved product label.

5.2.1.2.2 MK-3475 Dose Modifications

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

AEs associated with pembrolizumab exposure may have an immunologic etiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids, and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, or 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.

In addition, subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures, as described in Section 5.6.1, are also included in Table 3.

Table 3 Dose Modification and Toxicity Management Guidelines for Immune-related AEs Associated with MK-3475

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 Pneumonitis **- related AEs**	**Toxicity grade or conditions (CTCAEv4.0)**	**Action taken to pembrolizumab**	**irAE management with corticosteroid and/or other therapies**	**Monitor and follow-up**
	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 Pneumonitis **- 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 liothyronine) 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 Pneumonitis **- 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 MK-3475 Infusion Reaction Dose Modification and Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires 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 MK-3475 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

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

Dose increase of MK 3475 will not be permitted in individual subjects unless the 2 mg/kg dose of MK-3475 is dropped during the trial due to safety and/or efficacy concerns. If this occurs the Sponsor will inform the investigators and recommend to treat patients with 10mg/kg of MK-3475.

5.2.2 Timing of Dose Administration

MK-3475 will be administered at least 30 minutes prior to premedication for the chemotherapies or ipilimumab.

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 can be administered +/- 3 days of the targeted Day 1 for 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. MK-3475 should be administered prior to chemotherapy/immunotherapy. Please note that Day 1 of MK-3475 for the Dose Separation Phase in Cohort F is at Cycle 1 (Weeks 7 – 9) requiring a different schedule for PK/antibody samples as noted in the study flow chart (Section 6.2).

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

For subjects who experience disease progression, investigators may elect to interrupt treatment by deferring the decision to continue/discontinue treatment in the trial until confirmation of disease progression per RECIST 1.1 at least 28 days from the date of imaging demonstrating disease progression. Subjects for whom disease progression is not confirmed on subsequent imaging may resume treatment. Please see Section 5.8 for other exceptions.

5.2.2.1 MK-3475

MK-3475 will be administered as a 30-minute IV infusion Q3W. Sites should make every effort to target infusion timing to be as close to 30-minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30-minutes: -5 min/+10 min). Note that infusion time may take longer for subjects who exceed the upper weight boundary as listed in the Procedures Manual.

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

5.2.2.2 Paclitaxel

Paclitaxel 200 or 175 mg/m^2 will be administered as an IV infusion over 3 hours Q3W for 4 cycles. All subjects should be premedicated with oral or injectable steroids according to the approved product label and/or standard practice. Additional premedications should be administered as per standard practice.

5.2.2.3 Pemetrexed

Pemetrexed 500 mg/m^2 will be administered as an IV infusion over 10 minutes Q3W until progression or unacceptable toxicity. All subjects should receive the appropriate supplementation of vitamin B12 and folic acid according to the approved product label and/or standard practice. In addition, all subjects should receive the appropriate corticosteroid premedications as per the local approved label. Additional premedications should be administered as per standard practice.

5.2.2.4 Carboplatin

Carboplatin AUC 6 (for cohort A and B) or 5 (for cohorts C and G) mL/min will be administered as an IV infusion over 15-60 minutes Q3W for 4 cycles immediately after either paclitaxel or pemetrexed. Additional premedications should be administered as per standard practice.

5.2.2.5 Bevacizumab

Bevacizumab, 15 mg/kg, will be administered as an IV infusion over 30-90 minutes based on local approved product label Q3W. Additional premedications should be administered as per standard practice. Bevacizumab should be continued until progression of disease or unacceptable toxicity.

5.2.2.6 Ipilimumab

Ipilimumab 1 mg/kg will be administered as a 90-minute IV infusion (starting no sooner than 30 minutes after completion of MK-3475 infusion and after peak level of MK-3475 pharmacokinetic blood samples are drawn) for 4 cycles.

5.2.2.7 Erlotinib

Erlotinib 150 mg will be administered as an oral tablet daily. Additional premedications should be administered as per standard practice. Erlotinib should be continued until progression of disease or unacceptable toxicity.

5.2.2.8 Gefitinib

Gefitinib 250 mg will be administered as an oral tablet daily. Additional premedications should be administered as per standard practice. Gefitinib should be continued until progression of disease or unacceptable toxicity.

5.2.3 Trial Blinding/Masking

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

The subject-level PD-L1 biomarker results will be masked in the database to the investigator. Imaging data for the primary analysis will be centrally reviewed by independent radiologist(s) without knowledge of subject treatment assignment.

5.3 Randomization or Treatment Allocation

Randomization will occur centrally using an interactive voice response system/integrated web response system (IVRS/IWRS). There are 4 treatment arms that will be randomized: A, B, C and G. For cohorts A, B and C, subjects will be assigned randomly in a 1:1 ratio to receive chemotherapy plus 2 mg/kg MK-3475 or chemotherapy plus 10 mg/kg MK-3475.

For Cohort G1, subjects will be assigned randomly in a 1:1 ratio to receive carboplatin and pemetrexed plus/minus MK-3475 200 mg. Cohort G2 is optional and will be randomized the same as cohort G1.

5.4 Stratification

Randomization will be stratified according to the following factors:

Subjects in Cohort G1 will be stratified based on negative or positive PD-L1 tumor expression. Positive PD-L1 tumor expression is defined as Tumor Proportion Score (TPS) ≥1%. TPS <1% and PD-L1 unevaluable subjects will be included in the negative group.

5.5 Concomitant Medications/Vaccinations (Allowed & Prohibited)

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.

Palliative and supportive care is permitted during the course of the trial for underlying medical conditions and management of symptoms. Surgery or radiotherapy for tumor control is not permitted during the study; however, radiotherapy or procedures for symptom management is allowed.

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, crossover and Second Course Phases of this trial:

- 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; radiotherapy for symptom management is allowed.

- 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, chickenpox, yellow fever, nasal seasonal flu, nasal H1N1 flu, rabies, BCG, and typhoid vaccine.

- Prolonged therapy with systemic glucocorticoids (>7 days) for any purpose other than to modulate symptoms from an event of clinical interest or for use as a premedication for chemotherapeutic agents specified in the protocol. Brief, limited use of systemic corticosteroids (≤7 days) are permitted where such use is considered standard of care (e.g. as premedication for contrast allergy or for COPD exacerbation). Replacement doses of steroids (for example, prednisone 10 mg daily) are permitted while on study.

- Strong inhibitors of the CYP3A4 enzymes may not be used on Cohorts E & F (a common list of such agents may be found in Section 12.8)

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

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

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

5.6 Rescue Medications & Supportive Care

5.6.1 Supportive Care Guidelines

MK-3475

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of adverse events with potential immunologic etiology are outlined in the dose modification table (Table 3). Where appropriate, these guidelines include the use of oral or intravenous treatment with corticosteroids as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to MK-3475.

Note: if after the evaluation the event is determined not to be related to MK-3475, the investigator does not need to follow the treatment guidance.

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event. Suggested conditional procedures, as appropriate, can be found in the dose modification table.

5.6.2 Guidelines for Infusion-Reactions

See Section 5.2.1.2, Table 4.

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.

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

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

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

OR

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

OR

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

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

(1) practice abstinence[†] from heterosexual activity;

OR

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

Acceptable methods of contraception are‡:

Single method (one of the following is acceptable):

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

Combination method (requires use of 2 of the following):

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

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

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

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

5.7.3 Use in Pregnancy

If a female subject inadvertently becomes pregnant while on treatment in this study, the subject will immediately be removed from the study. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the Sponsor without delay and within 24 hours if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor. If a male subject impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to the Sponsor and followed as described above and in Section 7.2.2.

5.7.4 Use in Nursing Women

It is unknown whether MK-3475 is excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, subjects who are breastfeeding 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.

A subject must be discontinued from treatment but continue to be monitored in 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 RECIST 1.1, the subject should not receive further trial treatment on study except as indicated below. If a subject has unconfirmed progression of disease and is clinically stable, it is at the discretion of the investigator to continue treating the subject with the assigned

treatment per protocol until progression of disease is confirmed at least 28 days from the date of the scan suggesting progression of disease.

Exception 1) A subject who is clinically stable and has progression which is limited (defined as 1- 4 progressing lesions amenable to local ablative therapy) may, at the discretion of the investigator, continue assigned treatment per protocol after ablative therapy until further progression of disease is confirmed. No lung or liver lesions may be considered for ablation and at least one site of prior measurable disease should not be ablated. Protocol therapy will be interrupted until recovery from any toxicities due to ablation, not to exceed 12 weeks.

Exception 2) Subjects assigned to the chemotherapy arm in Cohort G1 will have the opportunity to crossover to receive MK-3475 monotherapy once they experience progression of disease (PD) defined by RECIST 1.1 and meet all crossover criteria defined in Section 7.1.5.5.

Clinical Stability is defined as:

1) Absence of symptoms and signs indicating clinically 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.
- 35 cycles (approximately 2 years) of uninterrupted delivery of MK-3475 every 3 weeks and no documented progression of disease
- 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 a MK-3475 treated subject attains an investigator-determined confirmed CR according to RECIST 1.1, has been treated for at least 6 months with MK-3475, and has at least 2 treatments with MK-3475 beyond the date when the initial CR was declared OR the subject has received the maximum administrations of MK-3475 as outlined above, the subject and investigator may consider stopping therapy with MK-3475. Subjects who discontinue MK-3475 and then experience radiographic disease progression according to RECIST 1.1 may 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.

Subjects will resume therapy at the dose and schedule when they previously stopped trial treatment unless that schedule has been discontinued, at which case subjects will resume therapy on the remaining schedule. Subjects who continue into the Second Course Phase will be administered MK-3475 at a fixed dose of 200 mg every 3 weeks for a maximum of 17 cycles.

Chemotherapy may be discontinued when a subject has received the maximum number of cycles permitted by the local regulatory authority. Maintenance pemetrexed may continue beyond Cycle 35 at the investigator's discretion and in accordance with local regulations until reaching a stopping criterion.

- 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 even if the patient started new antineoplastic treatment (serious adverse events will be collected for up to 90 days following cessation of Sponsor's product, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier 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

Subjects who received <90% of the MK-3475 infusion during the DLT window of observation as defined in 2.1.1 (e.g., because the infusion had to be discontinued due to an infusion reaction) and did not experience a DLT will not be taken into account in the assessment of the overall DLT rate for the particular dose level cohort and need to be replaced.

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 are discontinued and enrolled in a pembrolizumab extension study. Note that data cleaning and lock may take place before the end of trial. Subjects who may eventually be eligible for crossover who have not yet transitioned to pembrolizumab will be considered for the extension study on a case-by-case basis.

5.11 Clinical Criteria for Early Trial Termination

The trial will be stopped early 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.

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-progression Treatment

Investigators treating MK-3475 clinically-stable subjects 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 RECIST 1.1 at least 28 days from the date of imaging demonstrating disease progression. Subjects treated with MK-3475 for whom disease progression is not confirmed on subsequent imaging may resume treatment with MK-3475.

A subject who is clinically stable (defined in Section 5.8) and has confirmed progression which is limited (defined as 1- 4 progressing lesions amenable to local ablative therapy) may, at the discretion of the investigator, continue assigned treatment per protocol after ablative therapy until further progression of disease is confirmed. No lung or liver lesions may be considered for ablation and at least one site of prior measurable disease should not be ablated. Protocol therapy will be interrupted until recovery from any toxicities due to ablation, not to exceed 12 weeks.

Subjects assigned to the chemotherapy arm only in Cohort G will have the opportunity to crossover to receive MK-3475 monotherapy if they experience progression of disease (PD) defined by RECIST 1.1 and meet all crossover criteria defined in Section 7.1.5.5 for up to 35 treatment cycles (approximately 2 years) at the investigator's discretion.

5.13 Post MK-3475/Chemotherapies

After a subject stops the designated study treatment for one of the reasons described in Section 5.8, other than for a CR, the subject may be interested in pursuing other therapies. If investigators assess that the subject is fit for subsequent therapy, it is encouraged.

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

6.0 TRIAL FLOW CHART

6.1 Treatment Phase

	Screening (Visit 1)	Treatment Cycles[1]															End of Treatment
Treatment Cycle / Scheduled Time	-28 to -1	1	2	3	4	5	6	7	8	9	10	11	12	13	14 through 35	36+	Discontinuation Visit
Scheduling Window (Days):[2]			± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	
Administrative Procedures																	
Informed Consent	X																
Informed Consent for Future Biomedical Research (optional)	X[24]																
Inclusion/Exclusion Criteria	X																
Subject Identification Card	X																
Demographics and Medical History	X																
Prior and Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
NSCLC Disease Details and Prior Treatment	X																
Survival Status[27]		←----------															----------→
Clinical Procedures / Assessments																	
Review Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Full Physical Examination	X																X
Directed Physical Examination		X	X	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	X	X
12-Lead ECG	X																
ECOG Performance Status	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pulmonary Function Testing and DLCO	X																
Study Drug Administration																	
Paclitaxel/Carboplatin[16]		X	X	X	X												
Bevacizumab [14, 23]		X	X	X	X	X[23]	X	X	X	X	X	X	X	X	X		

	Screening (Visit 1)	Treatment Cycles[1]															End of Treatment
Treatment Cycle / Scheduled Time	-28 to -1	1	2	3	4	5	6	7	8	9	10	11	12	13	14 through 35	36+	Discontinuation Visit
Scheduling Window (Days**):**[2]			± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	
Pemetrexed[17, 23]		X	X	X	X	X[23]	X	X	X	X	X	X	X	X	X		
Carboplatin[17]		X	X	X	X												
Ipilimumab[18]		X	X	X	X												
Erlotinib[19, 22]		X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Gefitinib[20, 22]																	
MK-3475[21]		X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Laboratory Procedures / Assessments: analysis performed by local laboratory[26]																	
Pregnancy Test - Urine or Serum β-HCG [3]	X																
PT/INR and aPTT [4]	X [5]																
CBC with Differential[6]	X [5]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Comprehensive Serum Chemistry Panel[6]	X [5]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis[6, 7]	X [5]					X				X				X	X[7]		X
T3, FT3, FT4 and TSH [6, 8]	X [5]		X				X				X				X [7]		X
ALK Translocation Testing[15]	X																
EGFR Mutation Testing[15]	X																
Tumor PDL Expression	X																
Blood for Future Biomedical Research[25] (optional)		X															
MK-3475 Treatment Arm only: analysis performed by central laboratory																	
Pharmacokinetics [9]		X	X[10]	X			X			X				X	X [12]		X
Anti-MK-3475 Antibodies [11]		X	X	X			X			X				X	X [12]		X
Efficacy Measurements																	
Tumor Imaging [13]	X			X		X		X			X			X	X[13]	X[13]	X

	Screening (Visit 1)	Treatment Cycles[1]														End of Treatment
Treatment Cycle / Scheduled Time	-28 to -1	1	2	3	4	5	6	7	8	9	10	11	12	13	14 through 35	36+	Discontinuation Visit
Scheduling Window (Days):[2]			± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	
Tumor Biopsies / Archival Tissue Collection																	
Tumor Tissue Collection [25]	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). Imaging will be performed every 6 weeks (± 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 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.
4 Coagulation factors (PT/INR and aPTT) should be monitored closely throughout the trial for any subject receiving anticoagulant therapy.
5 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.
6 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.
7 Perform every 4 cycles after Cycle 13.
8 Thyroid function tests will be performed by a central laboratory only if the local laboratory is unable to perform this service.
9 MK-3475 treated subjects – Trough (predose) and peak (post-dose) samples will be collected at Cycles 1 and 2. A trough sample will be collected at Cycle 3, 6, 9, 13, and 17. All trough samples should be drawn within 24 hours before infusion of MK-3475 and at the same time as blood collection for anti-MK-3475 antibodies. The peak samples in Cycles 1 and 2 should be drawn within 30-minutes after the end of the infusion. Procedures for sample collection are described in the Procedures Manual.
10 MK-3475 treated subjects – An additional PK sample must be drawn between 24 and 96 hours after Cycle 2 dosing.
11 MK-3475 treated subjects – Draw samples for anti-MK-3475 antibodies within 24 hours before infusion of MK-3475 and at the same time as PK blood sample collection in Cycles 1, 2, 3, 6, 9, 13 and 17. After Cycle 17 collect samples every 8 cycles. Procedures for sample collection are described in the Procedures Manual.
12 Perform every 8 cycles after Cycle 17.
13 Performed every 6 weeks for the first 18 weeks, then every 9 weeks till the end of Year 1. Performed every 12 weeks subsequently until the subject experiences PD or initiates a new anticancer therapy. After the first documentation of progression (if the subject is clinically stable) or response per RECIST 1.1 repeat imaging for confirmation is required. Confirmatory imaging should be performed 4 to 6 weeks later. Timing of imaging scans should follow the calendar and not be adjusted for treatment delays.
14 Cohort B only, see Section 2.1 Trial Design.
15 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. See Section 7.1.3.4 for details on EGFR mutation testing.
16 Cohorts A and B only, see Section 2.1 Trial Design.
17 Cohort C and G only, see Section 2.1 Trial Design.
18 Cohorts D and H only, see Section 2.1 Trial Design.
19 Cohort E only, see Section 2.1 Trial Design.
20 Cohort F only, see Section 2.1 Trial Design.
21 Cohorts A, B, C, D, E, F and H. Chemotherapy + MK-3475 arm (exclude chemotherapy only arm) in Cohort G.
22 Tablets to be taken daily; will be dispensed at the beginning of each cycle.
23 May be continued as maintenance therapy after Cycle 4 at discretion of investigator.
24 Informed consent for Future Biomedical Research (FBR) samples must be obtained before the DNA sample is drawn. DNA sample for analysis should be obtained predose, on Day 1 (or with the next scheduled blood draw), as the last sample drawn, on allocated subjects only, or at a later date as soon as the informed consent is obtained. This sample should only be taken once from each subject. See Section 12.2 for guidance regarding the collection and management of specimens for FBR.

	Screening (Visit 1)	**Treatment Cycles[1]**															**End of Treatment**
Treatment Cycle / Scheduled Time	-28 to -1	1	2	3	4	5	6	7	8	9	10	11	12	13	14 through 35	36+	Discontinuation Visit
Scheduling Window (Days**):**[2]			± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	

25 Tumor tissue for biomarker analysis from an archival tissue sample or fresh biopsy of a tumor lesion not previously irradiated must be provided. Detailed instructions for tissue collection, processing and shipment are provided in the Procedures Manual. Any leftover tumor tissue will be stored for future research if the subject signs the optional FBR consent.

26 Subjects receiving chemotherapy only in cohort G1: require only CBC and chemistry panel after Cycle 6 (Week 18). This should be collected at the time of clinic visit for radiological scan.

27 After documented local site assessed disease progression, or the start of new anticancer treatment; contacts are approximately every 12 weeks by telephone. 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).

6.2 Cohort F Dose Separation Treatment Phase

	Screening (Visit 1)	Treatment Cycles(C)[1]															End of Treatment
Treatment Cycle / Scheduled Time	-28 to -1	1 Day 1	1 Week 3	1 Week 6	2	3	4	5	6	7	8	9	10	11	12	13	14 thru 35	Discon-tinuation Visit
Scheduling Window (Days):[2]			±3	±3	± 3	±3	±3	± 3	±3	± 3	± 3	±3	± 3	± 3	± 3	±3	± 3	
Administrative Procedures																		
Informed Consent	X																	
Informed Consent for Future Biomedical Research (optional)	X[19]																	
Inclusion/Exclusion Criteria	X																	
Subject Identification Card	X																	
Demographics and Medical History	X																	
Prior and Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
NSCLC Disease Details and Prior Treatment	X																	
Survival Status[20]		←----------																----------→
Clinical Procedures / Assessments																		
Review Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Full Physical Examination	X																	X
Directed Physical Examination		X	X	X	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	X	X	X
12-Lead ECG	X																	
ECOG Performance Status	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pulmonary Function Testing and DLCO	X																	

	Screening (Visit 1)	Treatment Cycles(C)[1]															End of Treatment
Treatment Cycle / Scheduled Time	-28 to -1	1 Day 1	1 Week 3	1 Week 6	2	3	4	5	6	7	8	9	10	11	12	13	14 thru 35	Discon-tinuation Visit
Scheduling Window (Days):[2]			±3	±3	± 3	±3	±3	± 3	±3	± 3	± 3	±3	± 3	± 3	± 3	±3	± 3	
Study Drug Administration																		
Gefitnib[16, 18]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
MK-3475[17]				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 [3]	X																	
PT/INR and aPTT [4]	X [5]																	
CBC with Differential[6]	X [5]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Comprehensive Serum Chemistry Panel[5]	X [5]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis[6,7]	X [5]							X				X				X	X[7]	X
T3, FT3, FT4 and TSH [6,8]	X [5]		X	X	X				X				X				X [7]	X
ALK Translocation Testing[14]	X																	
EGFR Mutation Testing[14]	X																	
Tumor PDL Expression	X																	
Blood for Future Biomedical Research[23] (optional)		X																
MK-3475 Treatment Arm only: analysis performed by central laboratory																		
Pharmacokinetics [9]				X	x[10]	X			X			X				X	X [12]	X
Anti-MK-3475 Antibodies [11]				X	X	X			X			X				X	X [12]	X
Efficacy Measurements																		
Tumor Imaging [13]	X			X		X		X		X			X			X	X	X
Tumor Biopsies / Archival Tissue Collection																		
Tumor Tissue Collection [19]	X																	

1	In general, assessments/procedures are to be performed on Day 1 and prior to the first dose of trial treatment unless otherwise specified. Patients will be treated with Gefitinib only for the first 6 weeks followed by the combination treatment of Gefitinib and MK-3475. Treatment cycles are 3 weeks (21-days) with the exception of Cycle 1 (42 days). Imaging will be performed every 6 weeks (± 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	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.
4	Coagulation factors (PT/INR and aPTT) should be monitored closely throughout the trial for any subject receiving anticoagulant therapy.
5	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.
6	After screening, 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 at each cycle. See Section 7.1.3 for details regarding laboratory tests.
7	Perform every 4 cycles after Cycle 13.
8	Thyroid function tests will be performed by a central laboratory only if the local laboratory is unable to perform this service.9 MK-3475 treated subjects – Trough (predose) and peak (post-dose) samples will be collected at Cycles 1 and 2. A trough sample will be collected at Cycle 3, 6, 9, 13, and 17. All trough samples should be drawn within 24 hours before infusion of MK-3475 and at the same time as blood collection for anti-MK-3475 antibodies. The peak samples in Cycles 1 and 2 should be drawn within 30-minutes after the end of the infusion. Procedures for sample collection are described in the Procedures Manual.
10	MK-3475 treated subjects – An additional PK sample must be drawn between 24 and 96 hours after Cycle 2 dosing.
11	MK-3475 treated subjects – Draw samples for anti-MK-3475 antibodies within 24 hours before infusion of MK-3475 and at the same time as PK blood sample collection in Cycles 1, 2, 3, 6, 9, 13 and 17. After Cycle 17 collect samples every 8 cycles. Procedures for sample collection are described in the Procedures Manual.
12	Perform every 8 cycles after Cycle 17.
13	Performed every 6 weeks for the first 24 weeks, then every 9 weeks till the end of Year 1. Performed every 12 weeks subsequently until the subject experiences PD or initiates a new anticancer therapy. After the first documentation of progression (if the subject is clinically stable) or response per RECIST 1.1 repeat imaging for confirmation is required. Confirmatory imaging should be performed 4 to 6 weeks later. Timing of imaging scans should follow the calendar and not be adjusted for treatment delays.
14	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. See Section 7.1.3.3 for details on EGFR mutation testing.
15	Patients will receive Gefitinib monotherapy for the first 6 weeks of treatment followed by the combination treatment of Gefitinib and MK-3475 (Cycle 1), see Section 2.1 Trial Design.
16	Patients will receive MK-3475 combined with Gefitinib (Cycle 1) after receiving 6 weeks of Gefitinib monotherapy, see Section 2.1 Trial Design.
17	Tablets to be taken daily; will be dispensed at the beginning of each treatment visit.
18	Informed consent for Future Biomedical Research (FBR) samples must be obtained before the DNA sample is drawn. DNA sample for analysis should be obtained predose, on Day 1 (or with the next scheduled blood draw), as the last sample drawn, on allocated subjects only, or at a later date as soon as the informed consent is obtained. This sample should only be taken once from each subject. See Section 12.2 for guidance regarding the collection and management of specimens for FBR.
19	Tumor tissue for biomarker analysis from an archival tissue sample or fresh biopsy of a tumor lesion not previously irradiated must be provided. Detailed instructions for tissue collection, processing and shipment are provided in the Procedures Manual. Any leftover tumor tissue will be stored for future research if the subject signs the optional FBR consent.
20	After documented local site assessed disease progression, or the start of new anticancer treatment; contacts are approximately every 12 weeks by telephone. 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).

6.3 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 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
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	X	X	X	
Laboratory Procedures/Assessments: analysis performed by local laboratory					
CBC with Differential [7]	X				
Comprehensive Serum 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 or before the initiation of a new antineoplastic treatment, whichever comes first. Subjects with an AE of Grade >1 will be further followed until the resolution of the AE to Grade 0-1 or until beginning of a new antineoplastic therapy, whichever occurs first. Subjects who are eligible per the requirements in Section 7.1.5.4 for treatment with 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. Follow-up Visit 1 should be scheduled approximately 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, follow-up visits should occur every 12 weeks (± 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, death or entering the Second Course Phase, whichever occurs first.

3 After documented local site assessed disease progression, or the start of new anticancer treatment; contacts are approximately every 12 weeks by telephone. 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).

4 Record all AEs occurring within 30 days after the last dose of trial treatment. Report all SAEs (related and unrelated to trial treatment) occurring within 90 days following cessation of treatment or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier. After this time, report only SAEs that are considered related to trial treatment.

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, as follows: every 12 weeks during year 1, 2 and 3, and every 6 months up to the end of year 5. Thereafter, imaging frequency will be based on local standards.
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.

6.4 Second Course Phase

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	14-17	Discon-tinuation Visit
Scheduling Window (Days**):**[2]		± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	
Administrative Procedures															
Eligibility Criteria	X														
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
MK-3475 Administration	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Survival Status[10]	←----------														----------→
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[7]	
Directed Physical Examination		X	X		X	X		X	X		X	X		X[7]	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[5]															
Pregnancy Test - Urine or Serum β-HCG [3]	X														
PT/INR and aPTT [4]	X														
CBC with Differential [6]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Comprehensive Serum Chemistry Panel [5]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis [6]	X				X				X				X	X [7]	X
T3, FT3, FT4 and TSH [6, 8]	X	X				X				X				X [7]	X
Efficacy Measurements															
Tumor Imaging [9]	X			X			X			X			X	X [12]	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). Imaging will be performed every 9 weeks (63 ± 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 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.

4	Coagulation factors (PT/INR and aPTT) should be monitored closely throughout the trial for any subject receiving anticoagulant therapy.
5	Laboratory tests for determining eligibility for Second Course Phase are to be performed within 10 days prior to the first dose of MK-3475. See Section 7.1.3 for details regarding laboratory tests.
6	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.
7	Perform at Cycle 13 and 17. Thyroid function tests should be performed at Cycle 14.
8	Thyroid function tests will be performed by a central laboratory only if the local laboratory is unable to perform this service.
9	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 9 weeks (63 ± 7 days) after the first dose of Second Course Phase trial treatment. The timing of imaging should follow calendar days and should not be adjusted for delays in cycle starts 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 may 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).
10	After documented local site assessed disease progression, or the start of new anticancer treatment; contacts are approximately every 12 weeks by telephone. 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).

6.5 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 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
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	X	X	X	
Laboratory Procedures/Assessments: analysis performed by local laboratory					
CBC with Differential [7]	X				
Comprehensive Serum 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 or before the initiation of a new antineoplastic treatment, whichever comes first. Subjects with an AE of Grade >1 will be further followed until the resolution of the AE to Grade 0-1 or until beginning of a new antineoplastic therapy, whichever occurs first. Subjects who are eligible per the requirements in Section 7.1.5.4 for treatment with 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. 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, follow-up visits should occur every 12 weeks (± 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 After documented local site assessed disease progression, or the start of new anticancer treatment; contacts are approximately every 12 weeks by telephone. 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).

4 Record all AEs occurring within 30 days after the last dose of trial treatment. Report all SAEs (related and unrelated to trial treatment) occurring within 90 days following cessation of treatment or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier. After this time, report only SAEs that are considered related to trial treatment.

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 until the start of a new antineoplastic therapy, documented disease progression, or death, whichever occurs first, as follows: every 12 weeks during year 1, 2 and 3, and every 6 months up to the end of year 5. Thereafter, imaging frequency will be based on local standards.
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.

6.6 Crossover Phase

(Only applicable for subjects randomized to Cohort G chemotherapy arm that have confirmation of PD and qualified for the crossover phase).

	Treatment Cycles[1]														End of Treatment
Treatment Cycle / Scheduled Time	1[7]	2	3	4	5	6	7	8	9	10	11	12	13	14 through 35	Discontinuation Visit
Scheduling Window (Days):[2]		± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	
Administrative Procedures															
Prior and Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Survival Status[10]	←----------→														
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
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
PT/INR and aPTT	X[3]														
Comprehensive Serum Chemistry Panel[9]	X[3]	X	X	X	X	X	X	X	X	X		X		X	X
Urinalysis[4]	X[3]				X				X				X	X[4]	X
T3, FT3, FT4 and TSH[4,5]	X[3]	X		X		X		X		X		X		X[4]	X
Efficacy Measurements															
Tumor Imaging[6]			X			X			X				X	X[6]	
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 and prior to the first dose of trial treatment for each cycle unless otherwise specified. Treatment cycles are 3 weeks (21-days). Imaging will be performed every 9 weeks (± 7 days) from the first dose of trial treatment for the first 6 months, and subsequently every 12 weeks, regardless of any treatment delays.
2	In general, the window for each visit is ± 3 days unless otherwise specified.
3	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.
4	Perform every 4 cycles beginning at Cycle 14 (Cycle 18, 22, 26, 30, and 34).
5	Thyroid function tests will be performed by a central laboratory only if the local laboratory is unable to perform this service.
6	Progressive disease is: 1) required for crossover, without exception, and 2) is based on RECIST 1.1. It is recommended that tumor response assessment be obtained every 9 weeks for the first 6 months and then every 12 weeks until PD or initiation of a new anticancer therapy. The image used to determine progressive disease can be used as the new baseline image for the crossover phase if 1) 30 days prior to receiving the first dose of MK-3475 monotherapy and 2) No study treatment between the image and first dose of MK-3475 monotherapy, otherwise a new baseline image must be performed prior to treatment of MK-3475 monotherapy. Timing of imaging scans should follow the calendar and not be adjusted for treatment delays.
7	Screening can initiate once progressive disease have been confirmed. Treatment with MK 3475 may not initiate until at least 21 days from the date of last dose of chemotherapy. Screening procedures may be completed during these 21 days. All procedures and assessments completed at the time of withdrawal from the main study may be used as appropriate for the start of the Crossover Phase of the study.
8	Treatment with MK 3475 may not initiate until at least 21 days from the last dose of chemotherapy. MK-3475 can be administered for up to 35 cycles (approximately 2 years).
9	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.
10	After documented local site assessed disease progression, or the start of new anticancer treatment; contacts are approximately every 12 weeks by telephone. 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 or qualified designee must obtain documented consent from each potential subject or each subject's legally acceptable representative prior to participating in a clinical trial or Future Biomedical Research.

7.1.1.1.1 General Informed Consent

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

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

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

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

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

7.1.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

The investigator or qualified designee will explain the Future Biomedical Research consent to the subject, answer all of his/her questions, and obtain written informed consent before performing any procedure related to Future Biomedical Research. 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 occur before the first dose of the new therapy. Once new antineoplastic therapy has been initiated the subject will move into survival follow-up.

7.1.1.7 Assignment of Screening Number

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

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

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

7.1.1.8 Assignment of Randomization Number

All eligible subjects will be randomly allocated 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 > 12 weeks require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on subject management.

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 Pharmacy Manual.

Standard of care therapy will be prepared and administered as per the approved product label.

7.1.2 Clinical Procedures/Assessments

7.1.2.1 Adverse Event (AE) Monitoring

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

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

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

7.1.2.2 Physical Exam

7.1.2.2.1 Full Physical Exam

The investigator or qualified designee will perform a complete physical exam during the screening period. 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.

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 diffusing capacity of the lungs for carbon monoxide (DLCO). 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 and Urinalysis)

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

Table 5 Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Blood	
Hemoglobin	Alkaline phosphatase	Glucose	Serum β-human chorionic gonadotropin (β-hCG)
Platelet count	Alanine aminotransferase (ALT)	Protein	Follicle stimulating hormone (FSH)
WBC (total and differential)*	Aspartate aminotransferase (AST)		Serum Triiodothyronine (T3)
	Bicarbonate or Carbon Dioxide	Microscopic exam, if abnormal results are noted	Free Triiodothyronine (FT3)
	Calcium		Free Thyroxine (FT4)
	Chloride		Serum thyrotropin (TSH)
	Creatinine		
	Glucose		
	Phosphorus		
	Potassium		
	Sodium		
	Total Bilirubin		
	Direct Bilirubin, if total bilirubin is elevated above the upper limit of normal		
	Total protein		
	Blood Urea Nitrogen		

*Absolute or percentage acceptable

7.1.3.2 Pharmacokinetic Evaluations

To evaluate the immunogenicity and exposure of pembrolizumab in this indication, sample collections for analysis of anti-pembrolizumab antibodies (ADA) and PK are currently planned as shown in the Trial Flowchart. Blood samples for PK and ADA collected may be stored only at this time. Further analysis may be performed if required. If ongoing PK and/or ADA sampling is deemed to be unnecessary by the Sponsor, it may be reduced or discontinued.

7.1.3.2.1 Blood Collection for Plasma 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.

7.1.3.3 Anti-MK-3475 Antibodies

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

7.1.3.4 Molecular Testing

Site must be able to provide documentation of subject's tumor EGFR mutation and ALK translocation status. Patients with known EGFR mutations do not need to get tested for ALK translocation. If the site is unable to provide this source documentation, then the Sponsor will offer this molecular testing of the tumor. Documentation of EGFR mutation status should include the specific test used (Roche cobas, Qiagen Therascreen, other lab-developed test), and the specific mutation detected. If an LDT is used, documentation should also describe which mutations are detected by the test. 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

7.1.4 Other Procedures

7.1.4.1 Withdrawal/Discontinuation

Subjects who discontinue/withdraw from study treatment prior to completion of the trial should be encouraged to continue to be followed for all remaining study visits and survival follow-up contacts.

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.

7.1.4.1.1 Withdrawal From Future Biomedical Research

Subjects may withdraw their consent for Future Biomedical Research and have their specimens and all derivatives destroyed. Subjects may withdraw consent at any time by contacting the principal investigator for the main trial. If medical records for the main trial are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@merck.com), and a form will be provided by the Sponsor to obtain appropriate information to complete specimen withdrawal. Subsequently, the subject's specimens will be removed from the biorepository and be destroyed. A letter will

be sent from the Sponsor to the investigator confirming the destruction. It is the responsibility of the investigator to inform the subject of completion of destruction. Any analyses in progress at the time of request for destruction or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research trial data and results. No new analyses would be generated after the request is received.

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

7.1.4.2 Blinding/Unblinding

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

7.1.4.3 Tumor Imaging

The initial tumor imaging will be performed within 30 days prior to the first dose of trial treatment. CT scans are the required modality for measurable disease unless a subject has a clinical condition e.g. severe contrast allergy, or the lesions are significantly better visualized through the use of an MRI. The same imaging technique must be used for a subject throughout the study. 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 6 weeks through Cycle 6 and every 9 weeks for the remainder of Year 1 after the first dose of trial treatment or more frequently if clinically indicated. On-study imaging will subsequently change to every 12 weeks until the subject experiences PD or initiates a new anticancer therapy. 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 RECIST 1.1, confirmatory scans should be performed 4 to 6 weeks later.

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 least 28 days later 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 (See exceptions in Section 5.8). If progression is not confirmed, then the subject should resume/continue trial treatment and have their next scan approximately 6 weeks from the date of the scan that first showed progression. When feasible, subjects should not be discontinued until progression is confirmed.

Subjects who move into the Second Course Phase will continue to have scans performed every 9 weeks.

Subjects who discontinue trial treatment for reasons other than disease progression should receive tumor imaging until confirmed disease progression or the start of a new antineoplastic therapy, whichever occurs first, as follows: every 12 weeks during year 1, 2 and 3, and every 6 months up to the end of year 5. Thereafter, imaging frequency will be based on local standards.

Disease progression for trial eligibility will be according to RECIST 1.1 criteria; Local reading (investigator assessment with site radiology reading) will be used to determine eligibility and for subject management.

The processes for image collection, processing and transmission to the central vendor are in the Site Imaging Manual (SIM).

7.1.4.4 Tumor Tissue Collection

Tumor tissue for biomarker analysis from formalin-fixed paraffin-embedded tumor tissue sample or newly obtained formalin-fixed biopsy of a tumor lesion not previously irradiated must be provided in the form of a tissue block or at least 10 unstained slides and received by the central vendor before randomization. If new scientific data emerge that indicate that an existing biopsy or surgical specimen is suboptimal for identification of subjects, then only new biopsies will be acceptable for determination of PD-L1 status. 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 encouraged. Note that if a tumor biopsy of a target lesion is obtained during eligibility assessment, it is preferred to obtain a new baseline scan.

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 subject signs informed consent.

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 28 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 28 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 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. 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 two-year follow-up period, he/she will be eligible to receive up to 12 months of therapy with MK-3475 in the Second Course Phase. After the Second Course Phase subjects should be followed for up to 2 years, with no option for re-treatment 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 or before the initiation of a new antineoplastic treatment, whichever comes first. Subjects with an AE of Grade >1 will be further followed until the resolution of the AE to Grade 0-1 or until beginning of a new antineoplastic therapy, whichever occurs first. Subjects who are eligible per the requirements in Section 7.1.5.4 for treatment with MK-3475 during the Second Course Phase may have up to 2 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 by radiologic imaging to monitor disease status. Follow-up Visit 1 should be scheduled approximately 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. 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 by radiologic imaging to monitor disease status. Follow-up Visit 1 should be scheduled approximately 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. 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 experiences disease progression by site assessment and verified by central imaging vendor review or starts a new anticancer therapy, the subject moves into the Survival Follow-Up Phase and should be contacted by telephone at least Q12W (more frequently if needed) from the last contact date to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

7.1.5.3.4 Survival Status

To ensure current and complete survival data are available at the time of database locks, updated survival status may be requested during the course of the study by the Sponsor. Upon Sponsor notification, all subjects who do not/will not have a scheduled study visit or study contact during the Sponsor-defined time period will be contacted for their survival status (excluding subjects that have previously recorded a 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 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 RECIST 1.1, were treated for at least 6 months with MK-3475, and received at least 2 treatments with MK-3475 beyond the date when the initial CR was declared. A CR by RECIST 1.1 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 at least 4 weeks later for the call of CR by RECIST 1.1 to be appropriate. So the subject 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 RECIST 1.1 after stopping their initial treatment with MK-3475 due to achievement of a confirmed CR.

OR

- Had SD, PR or CR and stopped MK-3475 treatment after 35 cycles (approximately 2 years) of study therapy for reasons other than disease progression or intolerability

AND

- Did not receive any anticancer treatment since the last dose of MK-3475.

- Continues to meet inclusion criteria 4, 5, 6, 7, 8 and 9.

- Does not meet exclusion criteria 2, 3, 4, 7, 9 to 15 and/or 19.

Subjects will be re-treated with MK-3475 200 mg every 3 weeks. An objective response or progression of disease that occurs during the Second Course Phase for a subject will not be counted as an event for the primary analysis of either endpoint in this trial.

7.1.5.5 Crossover for Subjects in Cohort G Chemotherapy Arm with Documented Disease Progression

Subjects in Cohort G who are randomized into the chemotherapy arm will have the opportunity to crossover to receive MK-3475 once they experience disease progression from the chemotherapy. Subjects who permanently discontinue chemotherapy due to an adverse event, withdraw consent, or for any reason other than progressive disease, will not be eligible for crossover. Crossover subjects must not initiate treatment with MK-3475 any earlier than 21 days after their last dose of chemotherapy regardless of the time of progression.

Crossover Qualifications

Subjects in Cohort G on the chemotherapy arm will be considered for crossover to MK-3475 after documented, progressive disease assessed based on RECIST 1.1 by the investigator followed by confirmation with the Sponsor. Crossover is optional and is at the discretion of the investigator (with the SPONSORs agreement). Subjects who meet the following criteria are eligible for crossover:

- Documentation of progressive disease will be defined as investigator assessment with confirmation with Sponsor per RECIST version 1.1
- Patients who have ablation due to limited PD as defined in Section 5.8 must have documented further progressive disease defined as investigator assessment with confirmation with Sponsor per RECIST version 1.1
- Chemotherapy induced adverse events (except alopecia) must have improved to CTCAE (Version 4.0) ≤Grade 1
- If a subject is unstable as a result of a new or progressing brain metastasis(es), the subject will not be eligible for crossover.
- ECOG Performance Status 0-1
- Subject has not received any other systemic chemotherapy other than the chemotherapy administered during the treatment phase.
- Received palliative radiotherapy of 30Gy or less ≥ 7 days before the first dose of crossover trial treatment.
- Patient has adequate organ function as indicated by the laboratory values in Section 5.1.2.

7.1.5.6 Crossover Assessments and Procedures

Crossover subjects must not initiate treatment with MK-3475 any earlier than 21 days after their last dose of chemotherapy regardless of the time of progression. The subject will then start the crossover phase as outlined in Crossover Flow Chart in Section 6.6. Screening procedures need to be completed within 28 days of confirmed progressive disease. All

procedures and assessments completed at the time of withdrawal from the main study may be used as appropriate for the start of the Crossover Phase of the study. The tumor image used to determine progressive disease can be used as the new baseline image for the Crossover phase if 1) 30 days prior to receiving the first dose of MK-3475 monotherapy and 2) No study treatment between the image and first dose of MK-3475 monotherapy, otherwise a new baseline image must be performed prior to MK-3475 monotherapy treatment. Subjects who crossover and then achieve a CR per RECIST 1.1 have the option to hold MK -3475 while continuing in the trial. Additional details are provided in Second Course Phase Section 7.1.5.4. Subjects who permanently discontinue the Crossover Phase will follow the same Post-Treatment Follow-up Phase Flow Chart provided in Section 6.3.

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).

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

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

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 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).

Although pregnancy and lactation are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them), including the pregnancy of a male subject's female partner that occurs during the trial or within 14 days of completing the trial. All subjects and female partners of male subjects who become pregnant must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

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

7.2.3 Immediate Reporting of Adverse Events to the Sponsor

7.2.3.1 Serious Adverse Events

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

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

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

- Is a new cancer (that is not a condition of the study);

- Is associated with an overdose.

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

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

7.2.3.2 Events of Clinical Interest

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

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

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

Events of clinical interest for this trial include:

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

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

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

Subjects should be assessed for possible ECIs prior to each dose. ECIs that occur to any subject from the date of first dose through 30 days following cessation of treatment 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 Adverse Event Reporting

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

Specifically, the suspected/actual events (as opposed to endpoints or endpoint components) covered in this exception are as follows: any event that is disease progression of the cancer under study which meets the criteria described in section 7.2.3.1. Note: as described in Section 7.2.3.1, any secondary primary cancer needs to be reported as a SAE.

For this protocol, the following MedDRA Preferred Term is considered suspected efficacy endpoint/endpoint event:

- Malignant Neoplasm Progression

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

7.2.4 Evaluating Adverse Events

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

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

For studies in which multiple agents are administered as part of a combination regimen, the investigator may attribute each adverse event causality to the combination regimen or to a single agent of the combination. In general, causality attribution should be assigned to the combination regimen (i.e., to all agents in the regimen). However, causality attribution may be assigned to a single agent if in the investigator's opinion, there is sufficient data to support full attribution of the adverse experience to the single agent.

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

7.2.5 Sponsor Responsibility for Reporting Adverse Events

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

7.3 TRIAL GOVERNANCE AND OVERSIGHT

7.3.1 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 Clinical Adjudication Committee

Clinical adjudication is not used in the study. For Cohort G1, all imaging will be collected for potential independent radiologists' review. Images will be assessed using RECIST 1.1 for determination of objective response rate (ORR) and progression-free survival (PFS). The use of independent radiologists' review will be determined based on the investigator assessed ORR and PFS.

8.0 STATISTICAL ANALYSIS PLAN

8.1 Statistical Analysis Plan Summary

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

8.1.1 Efficacy Analyses

The intention-to-treat (ITT) population that includes all randomized subjects will serve as the primary population for the analyses of efficacy data from randomized cohorts A, B, C, G1 and G2. The All-Subjects-as-Treated (ASaT) population that includes all treated subjects will serve as the primary population for the analyses of efficacy data from non-randomized cohorts D, E, F and H.

Part 1: Descriptive analyses will be provided. It is expected that 12 subjects will be treated at the RP2D.

Part 2: The primary efficacy endpoint is objective response rate (ORR) per RECIST 1.1 based on blinded independent central review. For cohort G1 only, the key secondary efficacy endpoint is progression-free survival (PFS) per RECIST 1.1 based on blinded independent central review. The Type I error rate alpha=2.5% (one-sided) over the multiple endpoints (primary ORR and key secondary PFS) will be controlled by a fixed-sequence, closed-testing procedure [73], stepping down from ORR to PFS. For cohort H, only the primary hypothesis

will be tested at alpha=5% (one-sided), and no multiplicity adjustment is planned. An outline of the analysis strategy for key efficacy endpoints is in Table 7.

Table 7 Summary of Analysis Strategy for Key Efficacy Endpoints in Part 2

Endpoint (Description, Time Point)	Statistical Method‡	Analysis Population	Missing Data Approach
Cohorts G1 and G2			
Objective response rate (RECIST 1.1) by blinded independent central review	Stratified Miettinen and Nurminen method	ITT	Subjects with missing data are considered as non-responders
PFS (RECIST 1.1) by blinded independent central review	Testing: Stratified Log-rank test Estimation: Stratified Cox model with Efron's tie handling method Kaplan-Meier method for PFS curve estimation in each treatment group	ITT	Censored according to Table 9.
Cohort H			
Objective response rate (RECIST 1.1) by blinded independent central review	Testing: exact Binomial test Estimation: Empirical proportion	ASaT	Subjects with missing data are considered as non-responders

8.1.2 Safety Analyses

The All-Subjects-as-Treated (ASaT) population will be employed for safety analyses. The ASaT population, consisting of all subjects who received at least 1 dose of study treatment, will be defined separately for Part 1 and Part 2 of the study. DLT will be summarized for Part 1 by dose level for each cohort. Descriptive tables that summarize the number and percentage of subjects that experience adverse events as categorized in the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 will be generated for each cohort in Part 2.

8.1.3 Power and Sample Size

In Cohorts A-F, the sample sizes depend primarily on clinical considerations rather than on statistical considerations. The details of the design are presented in Section 2.0. In summary, a randomized dose finding design will be used in Cohorts A, B and C with 12 subjects assigned to each of the 2 dose levels of MK-3475 combined with the chemotherapy.

Cohort G1 will randomize approximately 108 subjects with 1:1 ratio to either the MK-3475 in combination with chemotherapy arm or to the chemotherapy alone arm. The analysis will be conducted after all subjects have a minimum of 6 months follow-up. The study has at least 89% power to detect a 30% difference in ORR (30% in chemotherapy alone versus 60%

in MK-3475 in combination with chemotherapy) at α=2.5% (one-sided). An observed ORR difference of approximately 18.4% is needed to achieve a positive ORR outcome.

Cohort G2 is optional and event-driven by PFS (i.e., the number of subjects and follow-up time are subject to change but number of events is not); and plans to randomize approximately 60 subjects with 1:1 ratio to either the MK-3475 in combination with chemotherapy arm or to the chemotherapy alone arm, and will complete after approximately 44 events have been observed between the combination arm and the chemotherapy alone arm. With 44 events, the study has at least 84% power to detect a 0.4 hazard ratio at alpha=2.5% (one-sided) after taking a 5% discount for loss of information due to interval censoring.

Cohort H will enroll 32 subjects in a single arm of the MK-3475 and ipilimumab combination. The 12 subjects from cohort D expansion will be combined with subjects from cohort H in the analysis of objective response rate. With a total of 44 subjects, the study has approximately 90% power to detect a 20% difference (40% vs. 20% in historical control, obtained from MK-3475 PN001 data) in objective response rate at the 5% type I error rate (one-sided). A p-value of 5% approximately corresponds to an empirical objective response rate of 31% (14/44).

8.1.4 Subgroup Analyses

Subjects with high PD-L1 expression level are of special interest in this study. The treatment effect estimate and its 95% confidence interval for the primary and key secondary endpoints will be provided in the subgroup of subjects who are PD-L1 positive and PD-L1 negative. Other classification of interest will be explored as well

8.2 Statistical Analysis Plan

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, changes are made to primary and/or key secondary hypotheses, or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with ICH Guideline E-9). Changes to exploratory or other non-confirmatory analyses made after the protocol has been finalized, along with an explanation as to when and why they occurred, will be listed in the Clinical Study Report (CSR) for the study. Post hoc exploratory analyses will be clearly identified in the CSR. No separate Statistical Analysis Plan (SAP) will be issued for this Study.

8.2.1 Responsibility for Analysis/In-House Blinding

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

This trial is an open-label study. For Part 1, subjects, investigators, and Sponsor personnel will be aware of subject treatment assignments after each subject is enrolled and treatment is assigned. For Part 2 randomized cohorts, analyses or summaries generated by randomized treatment assignment and actual treatment received will be limited and documented. In

addition, the independent radiologist(s) will perform the central imaging review without knowledge of treatment group assignment.

The IVRS vendor will generate the randomized allocation schedule for study treatment assignment of cohort G1, and the Clinical Biostatistics department of the SPONSOR will generate the randomized allocation schedules for study treatment assignment of other cohorts for this protocol, and the randomization will be implemented in IVRS.

8.2.2 Hypotheses/Estimation

Objectives and hypotheses of the study are stated in Section 3.

8.2.3 Analysis Endpoints

8.2.3.1 Efficacy Endpoints

Primary

Objective response rate (ORR) – RECIST 1.1 by blinded independent central review

ORR is defined as the proportion of subjects who have achieved complete response (CR) or partial response (PR) according to RECIST 1.1 by blinded independent central review. Subjects with missing outcome on objective response will be considered non-responders.

Secondary

Progression-free Survival (PFS) – RECIST 1.1 by blinded independent central review

PFS is defined as the time from randomization (or the start of treatment when there is no randomization) to progressive disease (PD) or death, whichever occurs earlier, based upon RECIST 1.1 by blinded independent central review. Subjects without documented PD/death will be censored at the last disease assessment date. For cohorts G1 and G2, more censoring rules for sensitivity analyses are considered. See Section 8.2.5.1.2 for definition of censoring.

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

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

Overall survival (OS)

OS is defined as the time from randomization (or the start of treatment when there is no randomization) to death due to any cause. Subjects without documented death at the time of analysis will be censored at the date last known to be alive.

PFS/ORR – RECIST 1.1 by investigator assessment

PFS and ORR per RECIST 1.1 by investigator assessment are defined as specified for the respective endpoint.

PFS/ORR – modified RECIST 1.1 by investigator assessment

PFS and ORR per modified RECIST 1.1 are defined as specified for the respective endpoints using RECIST 1.1 above, with the exception that a confirmation assessment of PD (at least 4 weeks after the initial PD assessment) is required for subjects who remain on treatment following a documented PD per RECIST 1.1. Subjects who discontinue treatment following a documented PD assessment per RECIST 1.1 will be counted as having disease progression on the date of the documented PD assessment. See Section 8.2.5.1.2 for definition of censoring.

Exploratory

For cohort G1 only: exploratory endpoints will also include PFS2, PFS and OS following crossover to MK-3475.

In subjects who are randomized to chemotherapy only in cohort G1, PFS2 is defined as the time from randomization to subsequent disease progression following crossover to MK-3475, or death from any cause, whichever first. If progression after crossover to MK-3475 cannot be measured, a PFS event is defined as end or discontinuation of MK-3475 or death from any cause, whichever occurs first. Subjects alive and for whom a PFS event has not been observed will be censored at last disease assessment after crossover.

Time to progression following crossover to MK-3475 is defined as the time from the first dose of crossover therapy to the earliest documented disease progression (with respect to the last available tumor assessment prior to crossover). OS following crossover to MK-3475 is defined as the time from the first dose of crossover therapy to death due to any cause.

8.2.3.2 Safety Endpoints

The primary safety endpoint in Part 1 of the study is DLT. Safety will be monitored by cumulative data reviews throughout the trial. The toxicities and grades experienced by subjects who have received study treatment, including adverse events (AEs), serious adverse events (SAEs) and events of clinical interest (ECIs). Other safety measures evaluated in all parts of the study include laboratory safety assessments, ECGs, and vital signs and physical examinations. Safety measurements are as described in Section 7.

8.2.4 Analysis Populations

8.2.4.1 Efficacy Analysis Populations

The Intent-to-Treat (ITT) population will serve as the primary population for randomized cohorts A, B, C, G1 and G2. The ITT population consists of all randomized subjects with subjects analyzed in the treatment group to which they were randomized.

The All-Subjects-as-Treated (ASaT) population will serve as the primary population for non-randomized cohorts D, E, F and H. The ASaT population consists of all subjects who received at least one dose of study treatment with subjects analyzed in the treatment group corresponding to the study treatment they actually received.

Analysis of duration of response is based on all responders.

8.2.4.2 Safety Analysis Populations

The All-Subjects-as-Treated (ASaT) populations will be used for the analysis of safety data in this study. The ASaT population consists of all randomized subjects who received at least one dose of study treatment. Subjects will be included in the treatment group corresponding to the study treatment they actually received for the analysis of safety data using the ASaT population. For most subjects this will be the treatment group to which they are randomized. Subjects who take incorrect study treatment for the entire treatment period will be included in the treatment group corresponding to the study treatment actually received.

In Cohort G1, the primary safety comparison will be performed between MK-3475 in combination with chemotherapy arm and chemotherapy alone arm. Subjects who crossover to MK-3475 monotherapy will be censored at time of crossover and AEs occurred during treatment with MK-3475 monotherapy will be excluded from the primary safety analysis. An exploratory safety analysis will be conducted for the crossover population including all safety events from the date of first dose of MK-3475 after crossover.

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

For safety analysis related to DLT rate, the DLT evaluable population will be used. The DLT evaluable population consists of all DLT evaluable subjects. In order to be considered evaluable, the subject must complete the first cycle of therapy or discontinue from the trial due to a drug-related adverse event. Subjects who discontinue prematurely due to a non drug-related cause are not included in the DLT evaluable population.

8.2.5 Statistical Methods

8.2.5.1 Statistical Methods for Efficacy Analyses

8.2.5.1.1 Cohorts A-F

Subjects' ORR and PFS based on blinded independent central review and the investigator assessment per RECIST 1.1 along with other baseline characteristics will be analyzed using descriptive statistics.

8.2.5.1.2 Cohorts G1 and G2

The analysis strategy of key efficacy endpoints of Cohorts G1 and G2 are presented in Table 10.

Objective Response Rate (ORR)

ORR will be estimated as the number of responders as a percent of the number of participants in the ITT population. Its 95% confidence interval will be estimated using the Clopper-Pearson method [74]. For cohort G1, the stratified Miettinen and Nurminen's method [75] will be used to estimate the treatment difference and its 95% confidence interval with strata weighting by sample size. The stratification factor used for randomization of cohort G1 (i.e. PD-L1 expression positive vs. negative) will be applied to the analysis. For cohort G2, the non-stratified analyses will be provided. Subjects with missing outcome will be considered non-responders.

Duration of Response (DOR)

The non-parametric Kaplan-Meier plots/estimates and descriptive statistics will be provided. Subjects who are alive, have not yet progressed, have not initiated new anticancer treatment, have not had ≥ 2 consecutive missed disease assessments and have not been determined to be lost to follow-up are considered ongoing responders at the time of analysis. Censoring rules for DOR are summarized in Table 8 below.

Table 8 Censoring Rules for DOR

Situation	Date of Progression or Censoring	Outcome
No progression nor death, no new anticancer therapy initiated	Last adequate disease assessment	Censor (non-event)
No progression nor death, new anticancer therapy initiated	Last adequate disease assessment before new anticancer therapy initiated	Censor (non-event)
≥ 2 consecutive missed disease assessments at any time prior to progression or death	Last adequate disease assessment prior to ≥ 2 missed adequate disease assessments	Censor (non-event)
Death or progression after ≤ 1 missed disease assessments	PD or death	End of response (Event)
A missed disease assessment includes any assessment that is not obtained or is considered inadequate for evaluation of response. Subjects are considered to have an ongoing response if censored, alive, have not progressed, have not started a new anticancer therapy, have not had ≥ 2 consecutive missed disease assessments, and have not been determined to be lost to follow-up.		

Progression-Free Survival (PFS)

The non-parametric Kaplan-Meier method will be used to estimate the PFS curve in each treatment group. For Cohort G1, the stratified log-rank test will be used to test for treatment difference in PFS at one-sided alpha level of 2.5%. Stratified Cox proportional hazard model with Efron's tie handling method will be used to estimate the hazard ratio and its 95% confidence interval between the 2 arms. The same stratification factor used for randomization (i.e. PD-L1 expression positive vs. negative) will be applied to both the stratified log-rank test and the stratified Cox model. For cohort G2, no stratification will be applied in the analyses using the log-rank test or Cox proportional hazard 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 the first assessment at which PD is objectively documented per RECIST 1.1, regardless of discontinuation of study drug. Death is always considered as a confirmed PD event.

In order to evaluate the robustness of the PFS endpoint, 3 sensitivity analyses will be performed with a different set of censoring rules. Sensitivity analysis 1 is the same as the primary analysis except that it censors a subject's data at the last disease assessment without PD when there are 2 or more consecutive missed disease assessments. Sensitivity analysis 2 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. Sensitivity analysis 3 is the same as the primary analysis except that it censors a subject's data at the last disease assessment for subjects without

documented PD or death, regardless of initiation of new anticancer treatment. The censoring rules for primary and sensitivity analyses are summarized in Table 9. Additional PFS sensitivity analyses may be performed, including a PFS analysis using time to scheduled tumor assessment visit from randomization as opposed to actual tumor assessment time.

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
No PD and no death; ≥ 2 consecutive missed disease assessments	Censored at last disease assessment	Censored at last disease assessment prior to ≥2 consecutive missed visits	Censored at last disease assessment	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 consecutive missed disease assessments	Progressed at date of documented PD or death	Censored at last disease assessment prior to the ≥ 2 consecutive missed disease assessment	Progressed at date of documented PD or death	Progressed at date of documented PD or death

Overall Survival

The Kaplan-Meier method will be used to estimate the survival curves. For Cohort G1, 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 (i.e. PD-L1 expression positive vs. negative) will be applied to both the stratified log-rank test and the stratified Cox model. For cohort G2, no stratification will be applied in the analyses using the log-rank test or Cox proportional hazard model.

Since subjects in the control arm are expected to discontinue from the study earlier compared to subjects in the MK-3475 plus chemotherapy arm because of earlier onset of PD and they may switch to the MK-3475 treatment after the progressive disease, adjustment for the effect of crossover on OS may be performed based on recognized methods, e.g., the Rank Preserving Structural Failure Time (RPSFT) model proposed by Robins and Tsiatis (1989) [68], two stage model [69], etc., based on an examination of the appropriateness of the data to the assumptions required by the methods.

PFS and OS after Crossover

The same approaches as previously described for the primary PFS and primary OS analyses will be applied to subjects who crossover to MK-3475 after disease progression on the control arm (chemotherapy) in this study. The reference start time of PFS and OS is the time of first dose crossover therapy. Time to progression while on the control arm will be compared to the time to progression following crossover, where the time to progression following crossover is defined as the time from time of crossover to the earliest documented disease progression. The last available tumor assessment before crossover will serve as the baseline for disease assessment post crossover. If the number of events permits, time to progression before and after crossover will be summarized descriptively using the Kaplan-Meier method.

PFS2

The same approach as previously described for the primary PFS will be applied to compare PFS in subjects randomized to the MK-3475 in combination with chemotherapy arm and PFS2 in subjects randomized to chemotherapy alone arm.

Table 10 Analysis Strategy of Key Efficacy Endpoints of Cohorts G1 and G2

Endpoint/Variable (Description, Time Point)	Primary or Supportive Approach	Statistical Method	Analysis Population	Missing Data Approach
ORR (RECIST 1.1) by blinded independent central review	P	Stratified Miettinen and Nurminen method	ITT	Subjects with missing data are considered non-responders
PFS (RECIST 1.1) by blinded independent central review	P	Testing: Stratified Log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT	Censored according to rules in Table 9
DOR (RECIST 1.1) by blinded independent central review	P	Summary statistics using Kaplan-Meier method	All responders	Non-responders are excluded in analysis
OS	P	Testing: Stratified Log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT	Model based (censored at last date)

8.2.5.1.3 Cohort H

ORR will be the primary endpoint for efficacy assessment. The exact Binomial test will be used for testing ORR greater than the historical control rate of 20% at α=5% (one-sided). A 90% confidence interval and point estimate for ORR will be provided using the Clopper-Pearson method [74]. In addition, Kaplan-Meier plots and descriptive statistics of PFS, OS and DOR will be provided.

8.2.5.2 Statistical Methods for Safety Analyses

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

DLTs will be listed. Adverse experiences will be summarized as counts and frequencies for each dose level. Laboratory assessments, vital signs, and other safety endpoints will be summarized as appropriate.

Immune-related adverse events (irAEs) that are designated as AEs of special interest will be summarized in separate tables from other AEs, regardless of causality to study medication.

To properly account for the potential difference in follow-up time between the study arms, since the follow-up time is expected to be longer in the MK-3475 plus chemotherapy arm, AE incidence density adjusted for treatment exposure analyses may be performed as appropriate.

Time to Grade 3-5 AE

Exploratory analysis of Grade 3-5 AE may be performed on the time to first event. Time to first Grade 3-5 AE is defined as the time from the first day of study drug to the first event of Grade 3-5 AE. The Kaplan-Meier method will be used to estimate the curve of time to first Grade 3-5 AE. The treatment difference in time to first Grade 3-5 AE will be assessed by log-rank test. A Cox proportional hazard model with Efron's method of tie handling will be used to assess the magnitude of the treatment difference (i.e., the hazard ratio).

8.2.5.3 Summaries of Baseline Characteristics, Demographics, and Other Analyses

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

The correlation between PD-L1 expression levels and anti-tumor activity of MK-3475 in G1 will be explored, and a candidate cutoff point for PD-L1 expression level will be identified for enrollment of G2 based on both statistical and clinical considerations if a strong correlation between PD-L1 expression levels and anti-tumor activity is demonstrated.

Specifically, Kendal's Tau statistics will be used to explore the correlation between PD-L1 expression levels and tumor size reductions. Harrell's c-index [70, 71] will be used to explore the correlation between PD-L1 expression levels and PFS. Other methods as appropriate will also be considered.

8.2.6 Multiplicity

The overall type I error rate for cohort G1 is strictly controlled at 2.5% (one-sided) by fixed-sequence, a closed-testing procedure [73]. The closed-testing procedure will be applied to the primary hypothesis of ORR first. If the primary hypothesis is rejected at the α=2.5% level (one-sided), then testing will continue to the key secondary hypothesis of PFS. Nominal p-value for each endpoint will be reported, where applicable, regardless of the outcome of the closed-testing procedure dictated by the multiplicity strategy.

No multiplicity adjustment is planned for cohort H, as only one hypothesis of ORR is to be tested.

8.2.7 Sample Size and Power Calculations

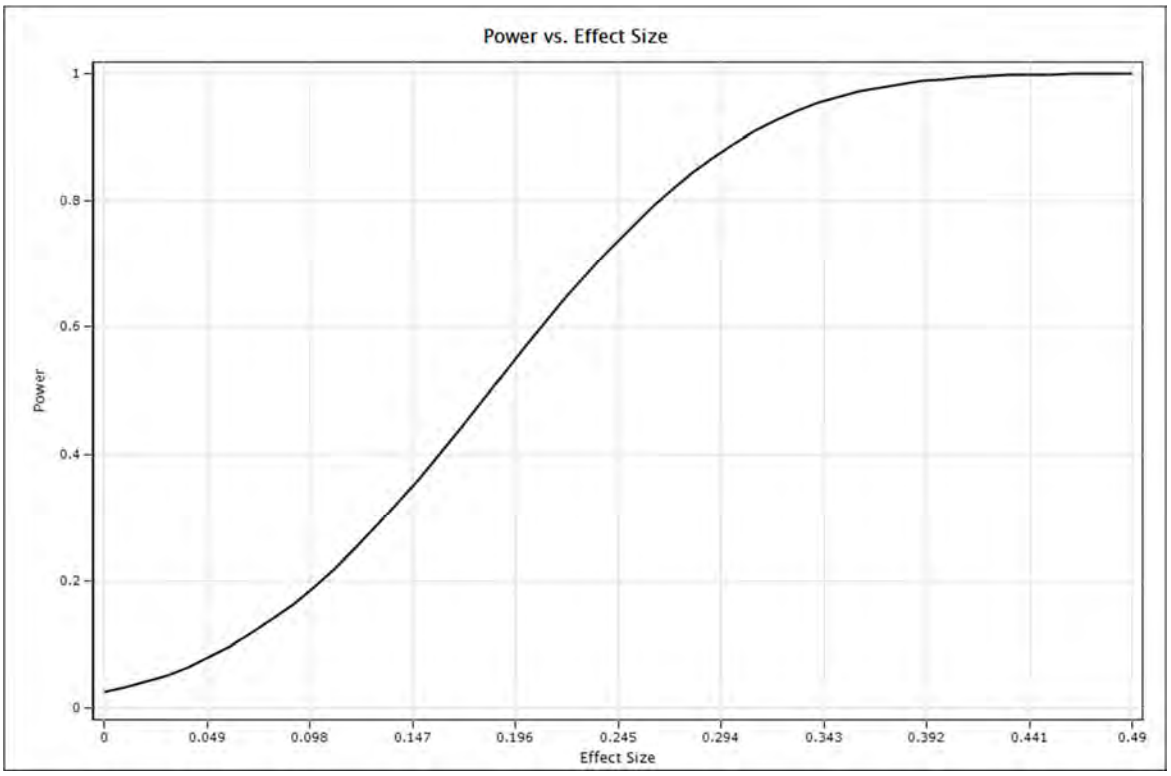
Cohorts A, B, C, D, E and F

The sample size of the study depends primarily on clinical considerations rather than on statistical considerations. Specifically, the final number of subjects enrolled in the study will depend on empirical DLT observations. However, it is estimated that around 144 subjects evaluable for safety and tolerability will be enrolled in the dose escalation and dose confirmation part (i.e., Part 1) of this study to adequately assess toxicity of MK-3475 in combination with chemotherapy, ipilimumab or TKI.

Cohort G1

Cohort G1 will randomize approximately 108 subjects with 1:1 ratio to either the MK-3475 in combination with chemotherapy arm or to the chemotherapy alone arm. The ORR analysis will be conducted after all subjects have a minimum of 6 months follow-up. The study has at least 89% power to detect a 30% difference in ORR (30% in chemotherapy alone versus 60% in MK-3475 in combination with chemotherapy) at α=2.5% (one-sided). The calculation is based on an asymptotic method proposed by Farrington and Manning (1990) [76]. An observed ORR difference of approximately 18.4% is needed to achieve a positive ORR outcome. Figure 2 summarizes power calculations for the primary hypothesis under various ORR difference assumptions.

Figure 2 Power for primary hypothesis under different effect size assumptions



At the time of the analysis, it is expected that approximately 68 PFS events will have been observed, and the study has overall ~81.5% power to detect a hazard ratio of 0.5 in MK-3475 in combination with chemotherapy vs. chemotherapy alone at alpha = 2.5% (one-sided). The power calculation is based on the following assumptions: 1) progression-free survival follows an exponential distribution with a median of 5.5 months in the chemotherapy alone arm, 2) hazard ratio between MK-3475 in combination with chemotherapy arm and chemotherapy alone arm is 0.5, 3) an enrollment period of 13 months, 4) at least 6 months follow-up after enrollment completion, and 5) a yearly dropout rate of 5%. A one-sided p-value of 2.5% approximately corresponds to an observed hazard ratio of 0.62 or less (approximately a 3.4-month or greater improvement over the median PFS from 5.5 months in the chemotherapy alone arm).

The sample size and power calculations of cohort G1 were performed using EAST 6.

Cohort G2

Cohort G2 is optional and event-driven by PFS (i.e., the number of subjects and follow-up time are subject to change but number of events is not); and plans to randomize approximately 60 subjects with 1:1 ratio to either the MK-3475 in combination with chemotherapy arm or to the chemotherapy alone arm, and will complete after approximately 44 events have been observed between the combination arm and the chemotherapy alone arm. With 44 events, the study has at least 84% power to detect a 0.4 hazard ratio at

alpha=2.5% (one-sided) after taking a 5% discount for loss of information due to interval censoring. The sample size and power were calculated using the normal approximation of log-rank test.

Cohort H

A total of 32 subjects will be enrolled in a single arm of the MK-3475 and ipilimumab combination (cohort H). Note that subjects from Cohort D expansion will be eligible to be combined with subjects from Cohort H in the analysis. With 44 subjects, the study has approximately 90% power to detect a 20% difference (40% vs. 20% in historical control) in objective response rate at the 5% type I error rate (one-sided). A p-value of 5% approximately corresponds to an empirical objective response rate of 31% (14/44).

8.2.8 Subgroup Analyses and Effect of Baseline Factors

The treatment effect within each of the following classification variables will be explored for G1 and G2: Age (≤ 65 vs. > 65 years), Sex (female vs. male), Race (white, non-white), and ECOG status (0 vs. 1). The consistency of the treatment effect will be assessed descriptively via summary statistics by category for the classification variables listed above.

8.2.9 Interim Analyses

No interim analysis is planned for this study.

8.2.10 Compliance (Medication Adherence)

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

8.2.11 Extent of Exposure

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

9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.1 Investigational Product

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

Clinical Supplies will be provided by the Sponsor as summarized in Table 11.

Table 11 Product Descriptions

Product Name & Potency	Dosage Form
MK-3475 25 mg/ml, 4 mL	Solution for infusion
Pemetrexed 500 mg / vial	Lyophilized powder for injection
Pemetrexed 100 mg / vial	Lyophilized powder for injection

All other supplies not indicated in Table 11 above will be provided locally by the trial site, subsidiary or designee, depending on local country operational or regulatory requirements.

Pemetrexed 500 or 100 mg / vial will be provided centrally by the Sponsor or locally by the trial site, subsidiary or designee, depending on local country operational or regulatory requirements.

All other supplies not indicated in Table 11 above will be provided centrally by the Sponsor or locally by the trial site, subsidiary or designee, depending on local country operational or regulatory requirements.

For any commercially available product that is provided by the trial site, subsidiary or designee every attempt will be made to source these supplies from a single lot/batch number. Per local guidelines the trial site may 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.

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

Open-label vials will be provided for this study. No kitting is required.

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. MK-3475 (name, strength or potency) is included in the label text; random code/disclosure envelopes or lists are not provided.

9.4 Storage and Handling Requirements

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

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

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

9.5 Returns and Reconciliation

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

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

9.6 Standard Policies

Trial site personnel will have access to a central electronic randomization system (IVRS/IWRS system) to allocate subjects, to assign MK-3475 to subjects and to manage the distribution of clinical supplies. Each person accessing the IVRS system must be assigned an individual unique PIN. They must use only their assigned PIN to access the system, and they must not share their assigned PIN with anyone.

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

10.1 Confidentiality

10.1.1 Confidentiality of Data

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

10.1.2 Confidentiality of Subject Records

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

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

10.1.3 Confidentiality of Investigator Information

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

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

2. hospital or clinic address and telephone number;

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

4. other professional documentation.

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

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

10.1.4 Confidentiality of IRB/IEC Information

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

10.2 Compliance with Financial Disclosure Requirements

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

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

10.3 Compliance with Law, Audit and Debarment

By signing this protocol, the investigator agrees to conduct the trial in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of Good Clinical Practice (e.g., International Council for Harmonisation of Technical Requirements for 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 multicenter 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.

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12.0 APPENDICES

12.1 Merck Code of Conduct for Clinical Trials

Merck*
Code of Conduct for Clinical Trials

I. Introduction

A. Purpose

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

B. Scope

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

II. Scientific Issues

A. Trial Conduct

1. Trial Design

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

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

2. Site Selection

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

3. Site Monitoring/Scientific Integrity

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

B. Publication and Authorship

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

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

III. Subject Protection

A. IRB/ERC review

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

B. Safety

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

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

C. Confidentiality

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

D. Genomic Research

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

IV. Financial Considerations

A. Payments to Investigators

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

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

B. Clinical Research Funding

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

C. Funding for Travel and Other Requests

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

V. Investigator Commitment

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

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

12.2 Collection and Management of Specimens for Future Biomedical Research

1. Definitions

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

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

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

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research

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

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

3. Summary of Procedures for Future Biomedical Research

a. Subjects for Enrollment

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

b. Informed Consent

Informed consent for specimens (i.e., DNA, RNA, protein, etc.) will be obtained during screening for protocol enrollment from all subjects or legal guardians, at a trial visit by the investigator or his or her designate. Informed consent for Future

Biomedical Research should be presented to the subjects on Visit 1. If delayed, present consent at next possible Subject Visit. Informed consent must be obtained prior to collection of all Future Biomedical Research specimens. Consent forms signed by the subject will be kept at the clinical trial site under secure storage for regulatory reasons. Information contained on the consent form alone cannot be traced to any specimens, test results, or medical information once the specimens have been rendered de-identified.

Subjects are not required to participate in the Future Biomedical Research in order to participate in the main trial. Subjects who decline to sign the Future Biomedical Research informed consent will not have the specimen collected nor will they be discontinued from the main trial.

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

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

c. eCRF Documentation for Future Biomedical Research Specimens

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

d. Future Biomedical Research Specimen Collections

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

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

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

4. Confidential Subject Information for Future Biomedical Research

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

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

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

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

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

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

5. Biorepository Specimen Usage

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

Analyses utilizing the Future Biomedical Research specimens may be performed by Merck, or an additional third party (e.g., a university investigator) designated by Merck. The investigator conducting the analysis will be provided with double coded specimens. Re-association of analysis results with corresponding clinical data will only be conducted by the Merck Entrusted Keyholder. Any contracted third party analyses will conform to the specific scope of analysis outlined in Future Biomedical Research protocol and consent. 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 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, and 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. Therefore, there will not be an additional risk for the subject.

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.

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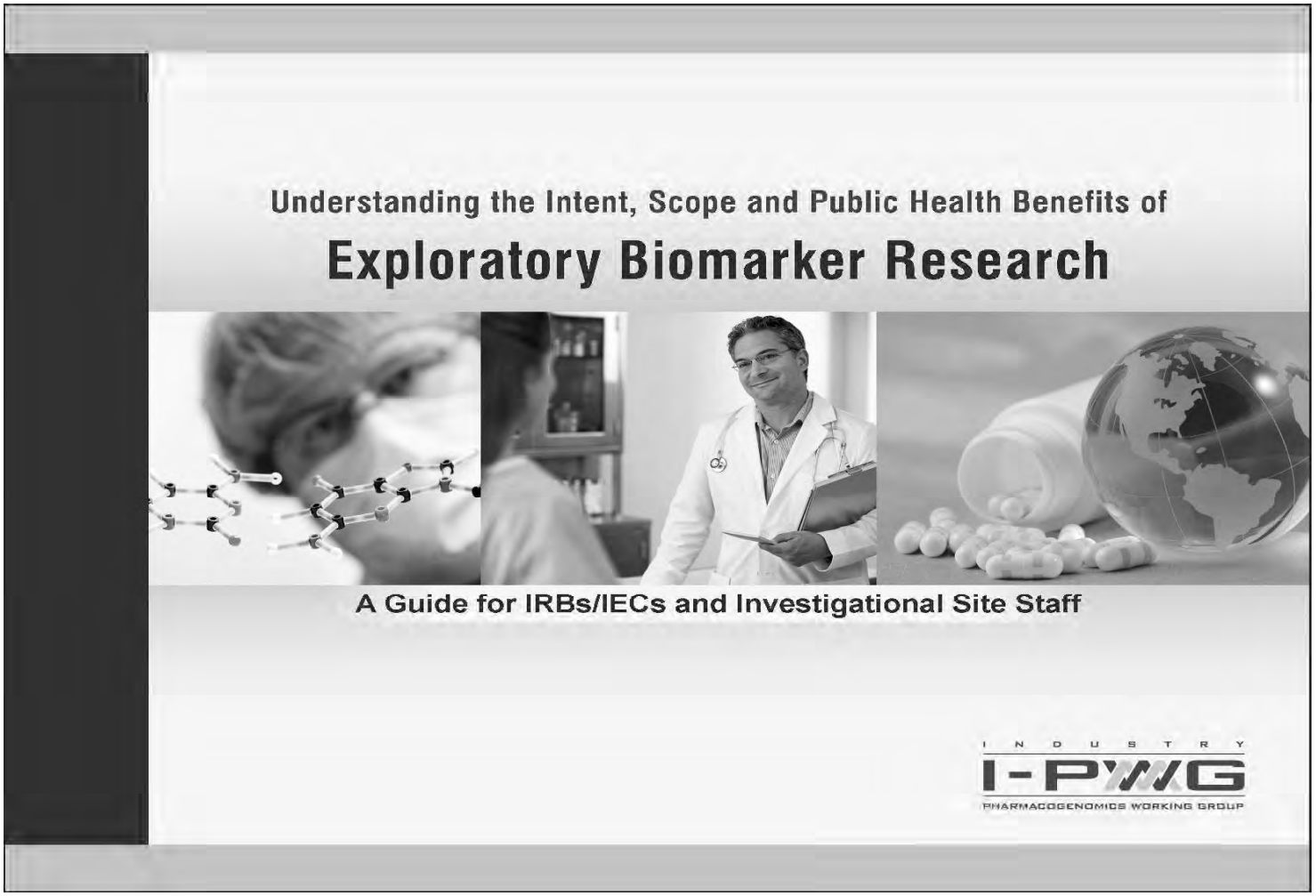
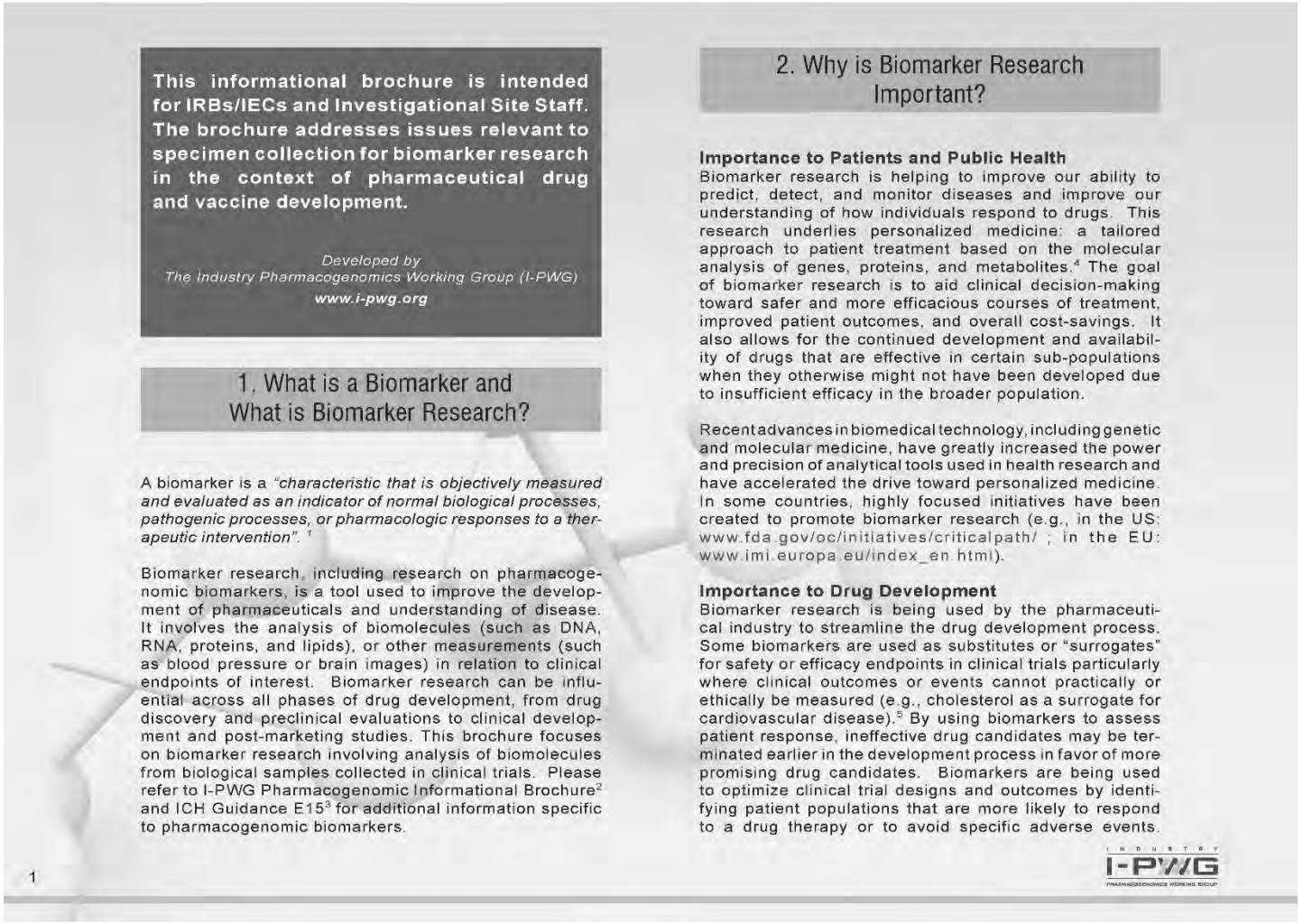
12.3 Understanding the Intent, Scope and Public Health Benefits of Exploratory Biomarker Research: A Guide for IRBs/IECs and Investigational Site Staff





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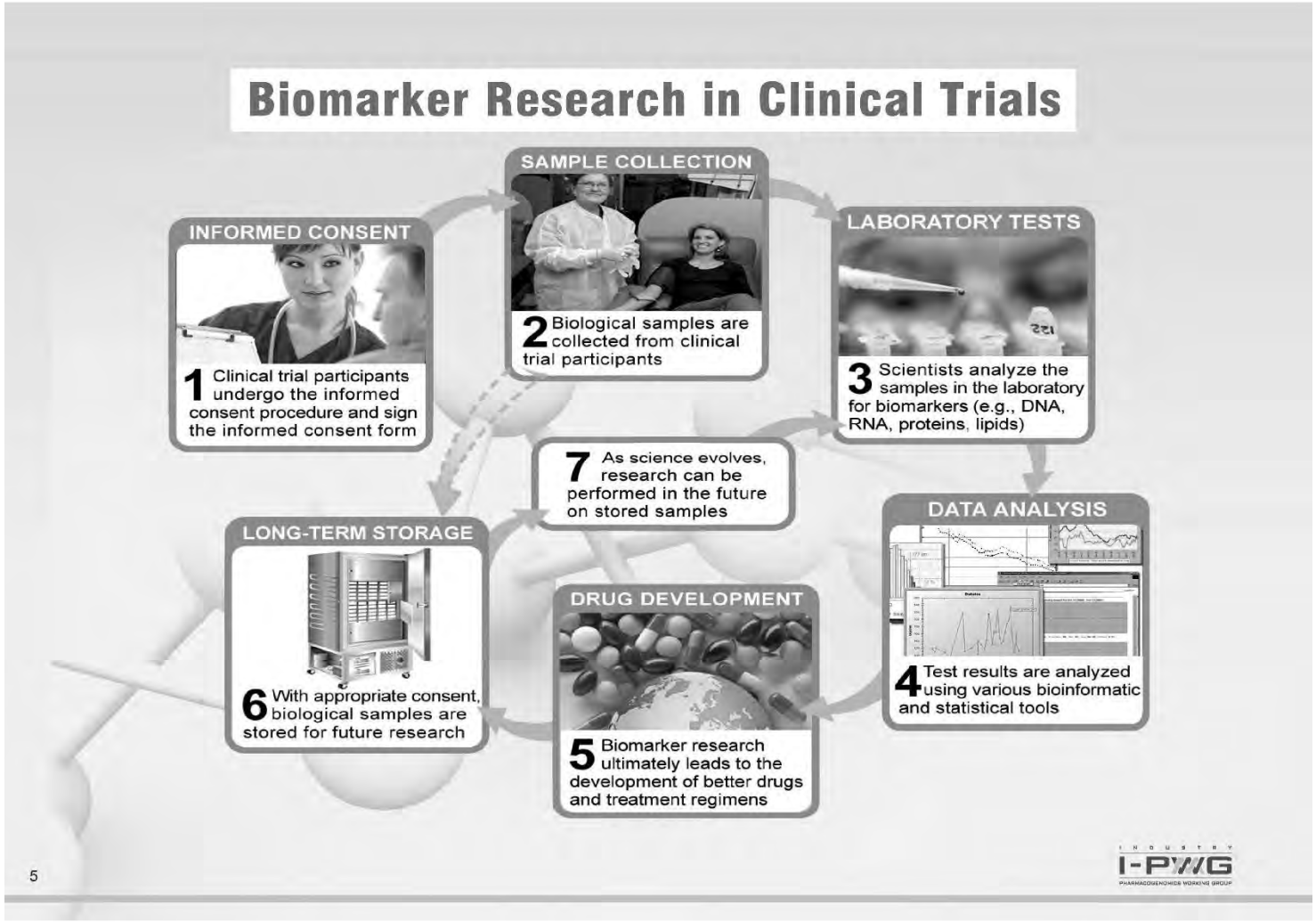
Biomarker Research in Clinical Trials
INFORMED CONSENT
1 Clinical trial participants undergo the informed consent procedure and sign the informed consent form
SAMPLE COLLECTION
2 Biological samples are collected from clinical trial participants
LABORATORY TESTS
3 Scientists analyze the samples in the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

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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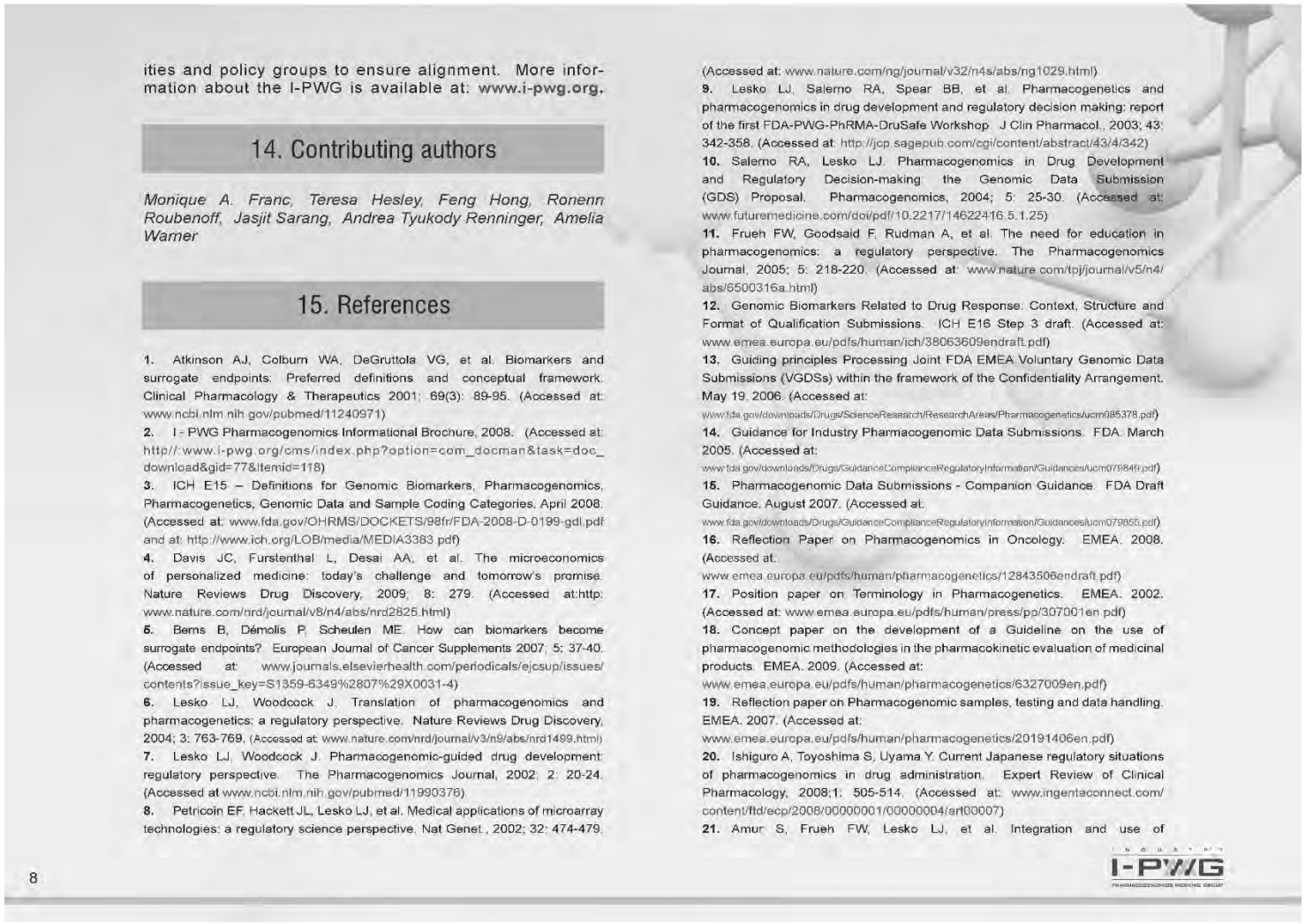

ities and policy groups to ensure alignment. More information about the I-PWG is available at: www.i-pwg.org.

14. Contributing authors

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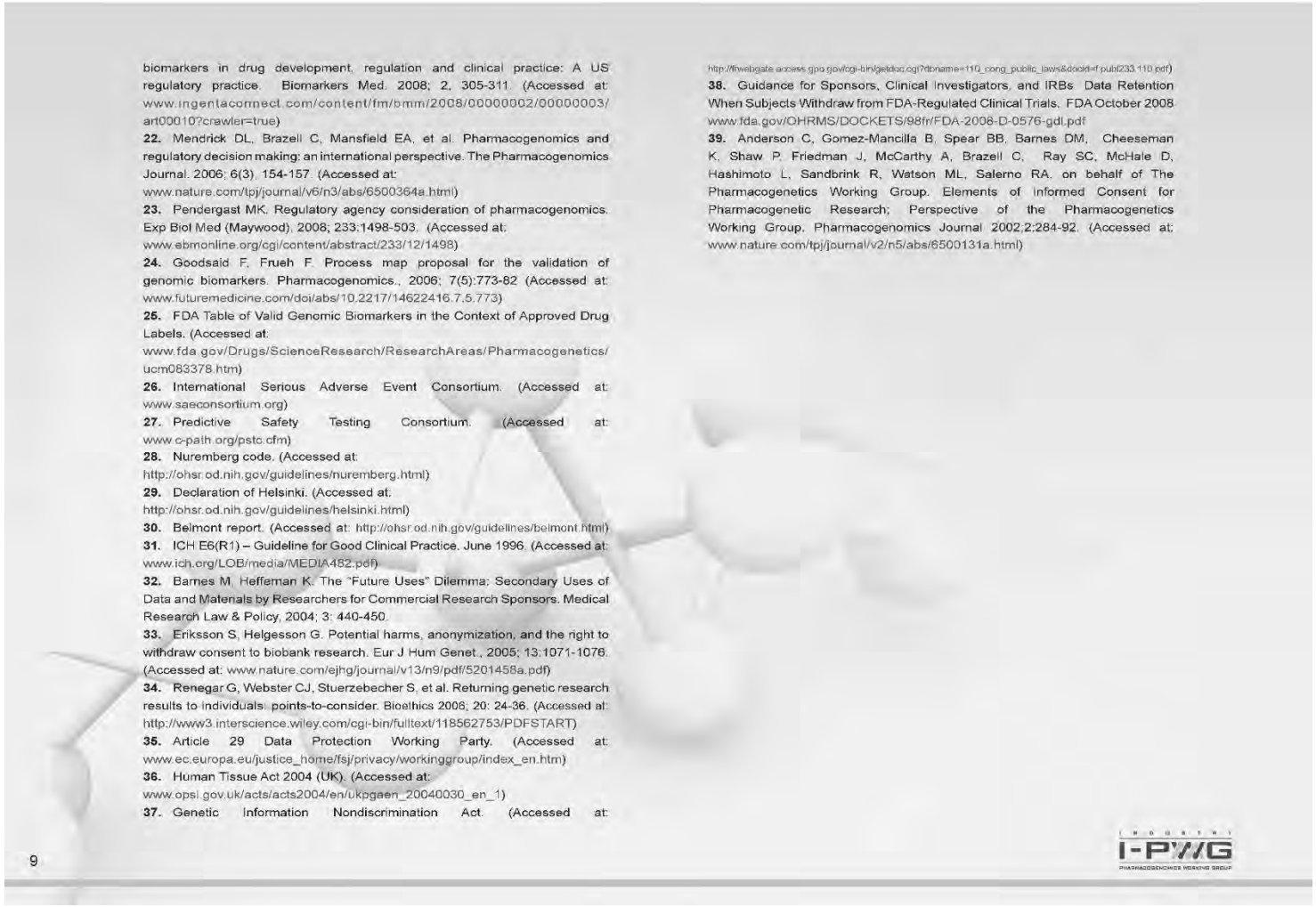


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12.4 Approximate Blood/Tissue Volumes Drawn/Collected by Trial Visit and by Sample Types

For approximate blood and tissue volumes, see Procedures Manual.

12.5 ECOG Performance Status

GRADE	ECOG PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	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	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4	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.

12.6 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)

12.7 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 may 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	
TITLE	
SIGNATURE	
DATE SIGNED	

13.2 Investigator

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

TYPED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	