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Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
(hereafter referred to as the Sponsor or Merck)
One Merck Drive
P.O. Box 100
Whitehouse Station, NJ 08889-0100, U.S.A.

Protocol-specific Sponsor Contact information can be found in the Investigator Trial File Binder (or equivalent).

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
EudraCT NUMBER: Not Applicable

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SUMMARY OF CHANGES

PRIMARY REASON(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
3.0 8.1.1 8.1.3 8.2.3.1 8.2.5.1.2 8.2.6 8.2.7	Objective(s) & Hypothesis(es) Efficacy Analyses Power and Sample Size Efficacy Endpoints Statistical Methods for Efficacy Analyses – Cohorts G1 and G2 Multiplicity Sample Size and Power Calculations	Cohort G1 – changed ORR as primary objective and hypothesis, PFS as key secondary, and DOR from exploratory to secondary. Updated the efficacy endpoints, analyses, statistical methods, multiplicity strategy, sample size and power sections in SAP accordingly. Alpha level for cohorts G1 and G2 was updated to 2.5% (one-sided).	Regulatory strategy update based on data from Cohort C (part 1).

ADDITIONAL CHANGE(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
1.0	Trial Summary	Duration of Participation was corrected to reflect the time the subject signs the ICF through the final protocol-specified contact.	Sentence revised to more accurately reflect the duration of participation.
5.1.2, 5.7.2	Inclusion Criteria, Contraception	Contraception requirements altered to allow certain single method contraception and abstinence when that is the subject's normal and preferred lifestyle.	Permitted contraception methods are anticipated to achieve a <1% failure rate based upon typical use.

5.2.1.1	Dose Selection	Removed provision that concomitant chemotherapies and immunotherapies are supplied by the site.	Revision reflects that pemetrexed may be centrally supplied by the Sponsor.
5.2.1.2	Dose Modifications (Escalation/Titration/Other)	Altered Table 4 footnote to require permanent discontinuation for recurrence of Grade 2 pneumonitis.	Modification is a more stringent safety requirement.
5.2.3	Trial Blinding/Masking	Added clarification on 1) investigator's blinding to PD-L1 biomarker results; and 2) blinded independent central review.	Missing in previous protocol amendment.
5.4	Stratification	Added clarification that PD-L1 tumor expression positive vs. negative is defined based on TPS 1% cut.	PD-L1 positive was defined as TPS >= 1% before cohort G1 enrollment started.
5.5.2	Prohibited Concomitant Medications	Altered to allow for brief, limited use of systemic corticosteroids (≤7 days) when use is considered standard of care.	Modification is consistent with standard of care.
5.5.2	Prohibited Concomitant Medications	Updated bullet to reflect that strong CYP3A4 inhibitors are only prohibited for patients on Cohorts E or F.	Strong CYP3A4 inhibitors may interact with gefitinib and erlotinib but are not known to interact with other trial treatments for this study.
5.10	Beginning and End of Trial	Removed specific cohorts from provision about data cleaning and data lock prior to LPLV.	Clarifies that other cohorts may clean data or lock prior to LPLV.
6.1, 6.2, 7.1.2.6	Trial Flow Charts, Pulmonary Function Testing	DLCO added to flow charts for Treatment Phase and Cohort F Dose Separation phase at Screening as a clarification. Replaced diffusion capacity with diffusing capacity of the lungs for carbon monoxide (DLCO).	Additions clarify that DLCO is required at screening.

6.4 7.1.4.3	Second Course Flow Chart Tumor Imaging	Removed and altered language that provided Second Course imaging instructions past Cycle 17.	Corrected mistakes that indicated treatment past 1 year.
6.6	Crossover Flow Chart	Provided schedule of tumor imaging	Correction of omission in previous protocol versions.
7.1.3.1	Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)	Updated Table 6 to include carbon dioxide, thyroid, and pregnancy testing.	Correction of omissions in previous protocol versions.
8.	Statistical Analysis Plan	Throughout the whole section: 1. Updated blinded independent radiologists' review to blinded independent central review 2. Updated endpoint description of response duration to duration of response	1. Program alignment 2. Duration of response is used in FDA guidance.
8.1.1 8.2.4.1	Efficacy Analyses Efficacy Analysis Populations	Clarified that ITT population for randomized cohorts, ASaT population for non-randomized cohorts, respectively, will be the primary analysis populations. Removed FAS population.	Regulatory requirement.
8.2.1	Responsibility for Analysis/In-House Blinding	1. Removed language that relates to restriction of study team's access to PD-L1 biomarker data. 2. Updated that allocation schedule for cohort G2, if initiated, will be generated by Clinical Biostatistics department of the SPONSOR.	1. PD-L1 cut point was defined before cohort G1 enrollment started. 2. G2 randomization, if initiated, is not going to be stratified.

8.2.3.1 8.2.5.1.2	Efficacy Endpoints Statistical Methods for Efficacy Analyses – Cohorts G1 and G2	1. Updated DOR definition, DOR censoring rules and definition of ongoing responders 2. Added one more scenario in the table for PFS censoring rules. Removed PFS sensitivity analysis using Finkelstein's likelihood-based score test for interval-censored data, and clarified that additional PFS sensitivity analyses may be performed. 3. Updated OS sensitivity analyses and clarified that adjustment for the crossover on OS may be performed based on recognized methods.	Program alignment.
8.2.5.2	Statistical Methods for Safety Analyses	Updated that for grade 3-5 AE analysis, only time-to-event analysis will be conducted. Clarified that exposure-adjusted AE analysis may be performed as appropriate.	Program alignment.
8.2.10	Compliance	Clarified that any deviation from protocol-directed administration will be reported.	Program alignment.
12.5	ECOG Performance Status	Corrected ECOG table to match the source publication.	Correction of table which had been slightly modified from the original publication.

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 48 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 5 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 will continue until two years of therapy have been administered, documented disease progression, unacceptable adverse event(s), intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw the subject, subject withdraws consent, pregnancy of the subject, noncompliance with the trial treatment or procedure requirements or administrative reasons. MK-3475 treated subjects who have been on therapy for ≥ six 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 24 months of treatments 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 and ECIs 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 three months, initiating a non-study cancer treatment and experiencing disease progression, until death, withdrawing consent, or becoming lost to follow-up.
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 multi-center, open-label, Phase I/II study of intravenous (IV) MK-3475 at two 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 two parts. Part 1 of the study will determine the recommended phase 2 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 24 months 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 in Year 2 with radiographic imaging to assess response to treatment. 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 two 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 24 months of treatments 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. 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 and ECIs 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.

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 $\leq$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 $\leq$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 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 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 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 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 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 six 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 2. 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 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 2. 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 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 2. 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 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 for a maximum of 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 24 months for the 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 one 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 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 24 months 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

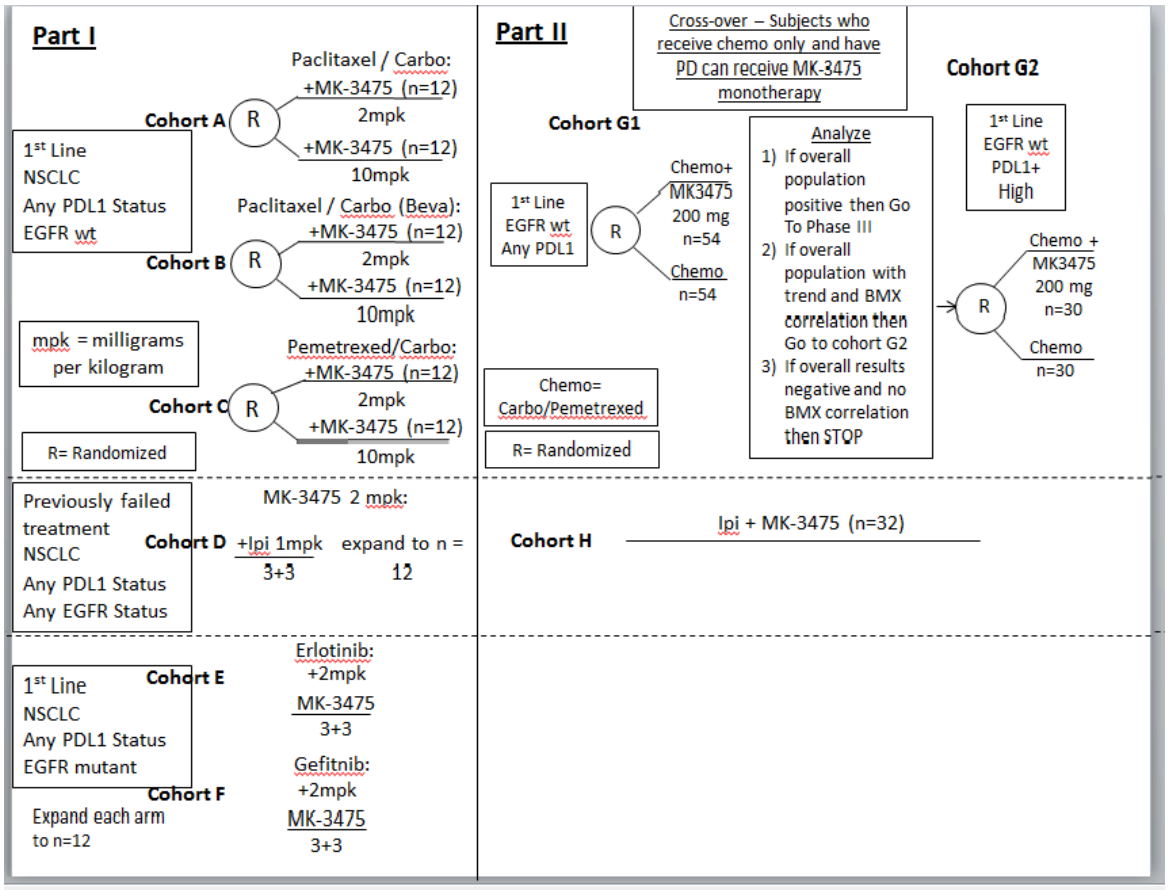

Figure 1 Trial Design

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).

Hypothesis:

- 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

Redacted

Redacted

Redacted

Redacted

Redacted

Redacted

Redacted

Redacted

Redacted

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
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)

Concomitant Chemotherapeutic agents

Refer to approved product label.

MK-3475

Adverse events (both non-serious and serious) associated with MK-3475 exposure may represent an immunologic etiology. These adverse events may occur shortly after the first dose or several months after the last dose of treatment. MK-3475 must be withheld for drug-related toxicities and severe or life-threatening AEs as per Table 3 and Table 3 below. See Section 7.2 and Events of Clinical Interest Guidance Document for supportive care guidelines, including use of corticosteroids.

Table 3 Dose Modification Guidelines for Drug-Related Adverse Events for Cohorts A, B, and C

Toxicity	Grade	Hold Treatment (Y/N)	Timing for restarting treatment	Dose/Schedule for restarting treatment	Discontinue Subject (after consultation with Sponsor)
Hematological Toxicity	1, 2	No	N/A	N/A	N/A
	3[a]	Yes	Toxicity resolves to Grade 0-1 or baseline	If 10 mg/kg, first reduce dose to 2 mg/kg.	Toxicity does not resolve within 12 weeks of last infusion *Permanent discontinuation should be considered for any severe or life-threatening event*
	4	Yes	Toxicity resolves to Grade 0-1 or baseline, only after discussion with the Sponsor	If 10 mg/kg, first reduce dose to 2 mg/kg.	
Non-hematological toxicity Note: Exception to be treated similar to grade 1 toxicity • Grade 2 alopecia • Grade 2 fatigue For additional information regarding Adverse Events with a potential Immune-Etiology reference Section 5.6.1 and 5.6.2.	1	No	N/A	N/A	N/A
	2	Consider withholding for persistent symptoms	Toxicity resolves to Grade 0-1 or baseline	*Clinical AE resolves within 4 weeks*: Same dose and schedule (reference Section 5.6.1.2 for recommendations regarding pneumonitis)	Toxicity does not resolve within 12 weeks of last infusion
	3,4	Yes	Toxicity resolves to Grade 0-1 or baseline	If 10 mg/kg, first reduce dose to 2 mg/kg.	Toxicity does not resolve within 12 weeks of last infusion *Permanent discontinuation should be considered for any severe or life-threatening event*

[a]Excluding Grade 3 neutropenia, anemia, and thrombocytopenia from the dose modification instructions.

Table 4 Dose Modification Guidelines for Drug-Related Adverse Events for Cohorts D, E, F, G, and H

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Treatment Discontinuation
Diarrhea/Colitis	2-3	Toxicity resolves to Grade 0-1.	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue
AST, ALT, or Increased Bilirubin	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose.
	3-4	Permanently discontinue	Permanently discontinue
Type 1 diabetes mellitus (if new onset) or Hyperglycemia	T1DM or 3-4	Hold MK-3475 for new onset Type 1 diabetes mellitus or Grade 3-4 hyperglycemia associated with evidence of beta cell failure.	Resume MK-3475 when patients are clinically and metabolically stable.
Hypophysitis	2-4	Toxicity resolves to Grade 0-1. Therapy with MK-3475 can be continued while endocrine replacement therapy is instituted	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
Hyperthyroidism	3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue
Hypothyroidism		Therapy with MK-3475 can be continued while thyroid replacement therapy is instituted	Therapy with MK-3475 can be continued while thyroid replacement therapy is instituted.
Infusion Reaction	2[a]	Toxicity resolves to Grade 0-1	Permanently discontinue if toxicity develops despite adequate premedication
	3-4	Permanently discontinue	Permanently discontinue
Pneumonitis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	3-4	Permanently discontinue	Permanently discontinue
Renal Failure or Nephritis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	3-4	Permanently discontinue	Permanently discontinue
All Other Drug-Related Toxicity[b]	3 or Severe	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue

Note: Permanently discontinue for any severe or Grade 3 drug-related AE (Grade 2 for pneumonitis) that recurs or any life-threatening event.

[a] If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose; Refer to Table 5– Infusion Treatment Guidelines for further management details.

[b] Patients with intolerable or persistent Grade 2 drug-related AE may hold study medication at physician discretion. Permanently discontinue study drug for persistent Grade 2 adverse reactions for which treatment with study drug has been held, that do not recover to Grade 0-1 within 12 weeks of the last dose.

Dosing interruptions are permitted in the case of medical / surgical events or logistical reasons not related to study therapy (e.g., elective surgery, unrelated medical events, patient

vacation, and/or holidays). Subjects should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the patient's study record.

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 pre-medicated with oral or injectable steroids according to the approved product label and/or standard practice. Additional pre-medications should be administered as per standard practice.

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 pre-medications as per the local approved label. Additional pre-medications 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 pre-medications 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 pre-medications 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 i.v. 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 pre-medications 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 pre-medications 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 four 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 inevaluable 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, cross-over 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 pre-medication 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 below and in greater detail in the

ECI guidance document. 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, the investigator is instructed to follow the ECI reporting guidance but does not need to follow the treatment guidance (as outlined in the ECI guidance document). Refer to Section 5.2.1 for dose modification.

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

- **Pneumonitis**:
    - For **Grade 2 events**, treat with systemic corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
    - For **Grade 3-4 events**, immediately treat with intravenous steroids. Administer additional anti-inflammatory measures, as needed.
    - Add prophylactic antibiotics for opportunistic infections in the case of prolonged steroid administration.
- **Diarrhea/Colitis**:
  Subjects should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus).
    - All subjects who experience diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion. For Grade 2 or higher diarrhea, consider GI consultation and endoscopy to confirm or rule out colitis.
    - For **Grade 2 diarrhea/colitis** that persists greater than 3 days, administer oral corticosteroids.
    - For **Grade 3 or 4 diarrhea/colitis** that persists > 1 week, treat with intravenous steroids followed by high dose oral steroids.
    - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
- **Type 1 diabetes mellitus (if new onset, including diabetic ketoacidosis [DKA]) or ≥ Grade 3 Hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA)**

- For **T1DM** or **Grade 3-4** Hyperglycemia
  - Insulin replacement therapy is recommended for Type I diabetes mellitus and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria.
  - Evaluate patients with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.

- **Hypophysitis**:
  - For **Grade 2** events, treat with corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
  - For **Grade 3-4** events, treat with an initial dose of IV corticosteroids followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

- **Hyperthyroidism or Hypothyroidism**:
  Thyroid disorders can occur at any time during treatment. Monitor patients for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders.
  - **Grade 2** hyperthyroidism events (and **Grade 2-4** hypothyroidism):
    - In hyperthyroidism, non-selective beta-blockers (e.g. propranolol) are suggested as initial therapy.
    - In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyroinine, is indicated per standard of care.
  - **Grade 3-4** hyperthyroidism
    - Treat with an initial dose of IV corticosteroid followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
- **Hepatic**:
  - For **Grade 2** events, monitor liver function tests more frequently until returned to baseline values (consider weekly).
    - Treat with IV or oral corticosteroids
  - For **Grade 3-4** events, treat with intravenous corticosteroids for 24 to 48 hours.
  - When symptoms improve to Grade 1 or less, a steroid taper should be started and continued over no less than 4 weeks.

- **Renal Failure or Nephritis**:
  - For **Grade 2** events, treat with corticosteroids.
  - For **Grade 3-4** events, treat with systemic corticosteroids.

- When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

5.6.2 Guidelines for Infusion Reactions

MK-3475

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

  Table 5 below shows treatment guidelines for subjects who experience an infusion reaction associated with administration of MK-3475.

Table 5 MK-3475 Infusion Reaction Treatment Guidelines

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

5.7 Diet/Activity/Other Considerations

5.7.1 Diet

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

5.7.2 Contraception

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

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

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

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

OR

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

OR

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

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

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

OR

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

Acceptable methods of contraception are[‡]:

Single method (one of the following is acceptable):

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

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

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

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

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

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study subjects of childbearing potential must adhere to the contraception requirement (described above) from the day of study medication initiation (or 14 days prior to the initiation of study medication for oral contraception) throughout the study period up to 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 breast-feeding are not eligible for enrollment.

5.8 Subject Withdrawal/Discontinuation Criteria

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

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

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

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 twelve 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 clinical significant progression of disease (including worsening of laboratory values) indicating disease progression.

2) No decline in ECOG performance status.

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

- Unacceptable adverse experiences as described in Section 5.2.1.2.
- Two years of uninterrupted delivery of MK-3475 every 3 weeks and no documented progression of disease
- 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 six months with MK-3475, and has at least two 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.

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

- The End of Treatment and Follow-up visit procedures are listed in Section 6 - Trial Flow Chart and Section 7.1.5 - Visit Requirements. After the end of treatment, each subject will be followed for a minimum of 30 days for adverse event monitoring even

if the patient started new antineoplastic treatment (serious adverse events and ECIs 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). Note that data cleaning and lock may take place before the end of trial.

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 twelve 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 2 years at the Investigators 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	Discontinuation Visit
Scheduling Window (Days):[2]			± 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
NSCLC Disease Details and Prior Treatment	X															
Clinical Procedures / Assessments																
Review Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Full Physical Examination	X															X
Directed Physical Examination		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
12-Lead ECG	X															
ECOG Performance Status	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pulmonary Function Testing 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	
Pemetrexed[17, 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	Discontinuation Visit
Scheduling Window (Days):[2]			± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	
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
Comprehensive Serum Chemistry Panel[6]	X [5]		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
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 (pre-dose) 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 3 months for Year 2. 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.
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.

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 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																	
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																	
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	

	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 Visit
Scheduling Window (Days):[2]			±3	±3	± 3	±3	±3	± 3	±3	± 3	± 3	±3	± 3	± 3	± 3	±3	± 3	
Laboratory Procedures / Assessments: analysis performed by local laboratory																		
Pregnancy Test - Urine or Serum β-HCG [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 (pre-dose) 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 3 months for Year 2. 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 7.1.3.4 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.

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 3 months after Month 6	Every 2 Months
Visit	Safety Follow-up Visit	Follow-up Visit 1	Follow-up Visit 2	Follow-up Visit 3 and beyond	Survival Follow-up Visit 1 and beyond
Scheduling Window	± 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]					X
Clinical Procedures/Assessments					
Review Adverse Events [4]	X	X	X	X	X
ECOG Performance Status	X	X	X		
Directed Physical Examination	X	X	X		
Vital Signs 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				
MK-3475 Treatment Arm only: analysis performed by central laboratory					
Anti-MK-3475 Antibodies [9]	X	X	X		
Pharmacokinetics [9]	X	X	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 every 3 months (± 7 days) by radiologic imaging to monitor disease status. Follow-up Visit 1 should be scheduled 3 months after the last dose of trial treatment. Follow-up Visit 2 should occur 6 months after the last dose of trial treatment. After Follow-up Visit 2 subjects only need to be assessed every 3 months (± 7 days) by radiologic imaging to monitor disease status, development of drug related SAEs and ECIs, and initiation of

new antineoplastic therapy. Unless otherwise noted in the flow chart, every effort should be made to collect subject information until the start of new antineoplastic therapy, disease progression, death or entering the Second Course Phase, whichever occurs first.

3 Once a subject experiences disease progression (and does not continue into the Second Course Phase) or starts a new antineoplastic therapy, the subject moves into the Survival Follow-up Phase and should be contacted by telephone every 2 months to assess for survival status and start of new antineoplastic therapy if applicable.

4 Record all AEs occurring within 30 days after the last dose of trial treatment. Report all SAEs (related and unrelated to trial treatment), ECIs, and irAEs occurring within 90 days 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 and ECIs that are considered related to trial treatment.

5 Vital signs to include temperature, pulse, respiratory rate, blood pressure and weight.

6 The same imaging technique should be used in a subject as was used earlier in the trial. Unless a subject enters the Second Course Phase, imaging should continue until the start of a new antineoplastic therapy, documented disease progression, or death, whichever occurs first. Subjects who enter the Second Course Phase will continue to be assessed every 3 months by radiologic imaging as described in the Second Course Phase Flow Chart.

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.

9 Every effort should be made to collect blood samples at the Safety Follow-up Visit, Follow-up Visit 1 and Follow-up Visit 2, until the start of new antineoplastic therapy, disease progression, death, or until the subject moves into the survival follow-up phase or Second Course Phase, whichever occurs first.

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 and beyond	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
Trial Treatment Administration	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Clinical Procedures / Assessments															
Review Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Full Physical Examination	X			X			X			X			X	X[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 [6]	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
Laboratory Procedures / Assessments: analysis performed by central laboratory															
Pharmacokinetics [9]	X	X[10]	X			X			X				X	X [9,]	X
Anti-MK-3475 Antibodies [11]	X	X	X			X			X				X	X [9,]	X
Efficacy Measurements															
Tumor Imaging [12, 13]	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 and 18..
8	Thyroid function tests will be performed by a central laboratory only if the local laboratory is unable to perform this service.
9	Trough (pre-dose) and peak (post-dose) samples will be collected at Cycles 1, 2 and 6. A trough sample will be collected at Cycle 3, 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, 2 and 6 should be drawn within 30-minutes after the end of the infusion. Procedures for sample collection are described in the Procedures Manual.
10	An additional PK sample must be drawn between 24 and 96 hours after Cycle 2 dosing.
11	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. Procedures for sample collection are described in the Procedures Manual.
12	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).
13	After the first documentation of progression (if the subject is clinically stable) or responses per RECIST 1.1, confirmatory imaging should be performed 4 to 6 weeks later.

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 3 months after Month 6	Every 2 Months
Visit	Safety Follow-up Visit	Follow-up Visit 1	Follow-up Visit 2	Follow-up Visit 3 and beyond	Survival Follow-up Visit 1 and beyond
Scheduling Window	± 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]					X
Clinical Procedures/Assessments					
Review Adverse Events [4]	X	X	X	X	X
ECOG Performance Status	X	X	X		
Directed Physical Examination	X	X	X		
Vital Signs 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				
Laboratory Procedures/Assessments: analysis performed by central laboratory					
Anti-MK-3475 Antibodies [9]	X	X	X		
Pharmacokinetics [9]	X	X	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 every 3 months (± 7 days) by radiologic imaging to monitor disease status. Follow-up Visit 1 should be scheduled 3 months after the last dose of trial treatment. Follow-up Visit 2 should occur 6 months after the last dose of trial treatment. After Follow-up Visit 2 subjects only need to be assessed every 3 months ± 7 days) by radiologic imaging to monitor disease status, development of drug related SAEs and ECIs, and initiation of new antineoplastic therapy. Unless otherwise noted in the flow chart, every effort should be made to collect subject information until the start of new antineoplastic therapy, disease progression or death, whichever occurs first.

3 Once a subject experiences disease progression or starts a new antineoplastic therapy, the subject moves into the Survival Follow-up Phase and should be contacted by telephone every 2 months to assess for survival status and start of new antineoplastic therapy if applicable.

4 Record all AEs occurring within 30 days after the last dose of trial treatment. Report all SAEs (related and unrelated to trial treatment), ECIs, and irAEs occurring within 90 days 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 and ECIs that are considered related to trial treatment.

5 Vital signs to include temperature, pulse, respiratory rate, blood pressure and weight.

6 The same imaging technique should be used in a subject as was used earlier in the trial. Subjects, who discontinue trial treatment due to reasons other than disease progression, should continue to be assessed every 3 months(± 7 days) by radiologic imaging until the start of a new antineoplastic therapy, documented disease progression, or death, whichever occurs first.

7 See Section 7.1.3 for list of laboratory tests.

8 Analysis will be performed by a central laboratory only if the local laboratory is unable to perform this service.

9 Every effort should be made to collect blood samples at the Safety Follow-up Visit, Follow-up Visit 1 and Follow-up Visit 2 until the start of new antineoplastic therapy, disease progression or death, whichever occurs first.

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
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
MK-3475 Treatment Arm only: analysis performed by central laboratory															
Pharmacokinetics[10]	X	X	X			X			X				X	X[11]	X
Anti-MK-3475 Antibodies[12]	X	X	X			X			X				X	X[11]	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 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 after cycle 13.
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 till the end of year 2. The image used to determine progressive disease can be used as the new baseline image for the cross-over 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 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	MK-3475 treated subjects – Trough (pre-dose) 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.
11	MK-3475 treated subjects – An additional PK sample must be drawn between 24 and 96 hours after Cycle 2 dosing.
12	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.

7.0 TRIAL PROCEDURES

7.1 Trial Procedures

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

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

7.1.1 Administrative Procedures

7.1.1.1 Informed Consent

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

7.1.1.1.1 General Informed Consent

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

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

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

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

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

7.1.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

The investigator or qualified designee will explain the Future Biomedical Research consent to the subject, answer all of his/her questions, and obtain written informed consent before performing any procedure related to the Future Biomedical Research sub-trial. A copy of the informed consent will be given to the subject.

7.1.1.2 Inclusion/Exclusion Criteria

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

7.1.1.3 Subject Identification Card

All subjects will be given a Subject Identification Card identifying them as participants in a research trial. The card will contain trial site contact information (including direct telephone numbers) to be utilized in the event of an emergency. The investigator or qualified designee will provide the subject with a Subject Identification Card 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. Following the guidance described in Section 7.2.3.2., certain irAEs should also be reported to the Sponsor as ECIs. (See the separate guidance document in the administrative binder regarding the identification, evaluation and management of irAEs and ECIs).

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

7.1.2.2 Physical Exam

7.1.2.2.1 Full Physical Exam

The Investigator or qualified designee will perform a complete physical exam during the screening period. Clinically significant abnormal findings should be recorded as medical history. The timepoints for full physical exam are described in Section 6 - Trial Flow Chart. After the first dose of trial treatment new clinically significant abnormal findings should be recorded as AEs.

7.1.2.2.2 Directed Physical Exam

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

7.1.2.3 Vital Signs

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

7.1.2.4 12-Lead Electrocardiogram (ECG)

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

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 6.

Table 6 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

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

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 measureable 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 change to every 3 months in Year 2. 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 discontinue trial treatment for reasons other than disease progression should receive tumor imaging every 3 months until the subject experiences confirmed disease progression or starts a new antineoplastic therapy. Subjects who move into the Second Course Phase will continue to have scans performed every 9 weeks.

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 ten 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. Subjects will be followed for up to 2 years in Follow-up. If the subject experienced a CR, PR, or SD during the treatment Phase on 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 two years, with no option for retreatment with MK-3475 on study.

7.1.5.3.1 Safety Follow-up Visit

The mandatory Safety Follow-Up Visit should be conducted approximately 30 days after the last dose of trial treatment 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.

7.1.5.3.2 Follow-up Visits

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

7.1.5.3.3 Survival Follow-up

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

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 12 months 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 six months with MK-3475, and received at least two treatments with MK-3475 beyond the date when the initial CR was declared. A CR by 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 24 months of study therapy for reasons other than disease progression or intolerability

AND

- Did not receive any anti-cancer 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 at the same dose as when they last received MK-3475. 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 chemotherapies 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 7 for additional details regarding each of the above criteria.

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

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

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

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

7.2.3.2 Events of Clinical Interest

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

For the time period beginning when the consent form is signed until treatment allocation/randomization, any ECI, or follow up to an ECI, that occurs to any subject must be

reported within 24 hours to the Sponsor if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

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

Events of clinical interest for this trial include:

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

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

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

A separate guidance document has been provided entitled "MK-3475 Events of Clinical Interest and Immune-Related Adverse Event Guidance Document". This document can be found in the administrative binder and provides guidance regarding identification, evaluation and management of ECIs and irAEs. Additional ECIs are identified in this guidance document and also need to be reported to the SPONSOR within 24 hours of the event.

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

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

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

7.2.3.3 Protocol-Specific Exceptions to Serious 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 7 Evaluating Adverse Events
An investigator who is a qualified physician, will evaluate all adverse events as to:

V4.0 CTCAE Grading	**Grade 1**	**Mild; asymptomatic or mid symptoms; clinical or diagnostic observations only; intervention not indicated.**
	Grade 2	**Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.**
	Grade 3	**Severe or medically significant but not immediately life-threatening; hospitalization or prolongation or hospitalization indicated; disabling; limiting self-care ADL.**
	Grade 4	**Life threatening consequences; urgent intervention indicated.**
	Grade 5	**Death related to AE**
Seriousness	A serious adverse event is any adverse event occurring at any dose or during any use of Sponsor's product that:	
	†**Results in death**; or	
	†**Is life threatening; or** places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred (Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.); or	
	†**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or	
	†**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization [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 8.

Table 8 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 10
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 two 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

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 anti-cancer 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 9 below.

Table 9 Censoring Rules for DOR

Situation	Date of Progression or Censoring	Outcome
No progression nor death, no new anti-cancer therapy initiated	Last adequate disease assessment	Censor (non-event)
No progression nor death, new anti-cancer therapy initiated	Last adequate disease assessment before new anti-cancer therapy initiated	Censor (non-event)
≥ 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 anti-cancer 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 two 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, three 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 10.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 10 Censoring Rules for Primary and Sensistivity 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 11 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 10
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 ECIs (irECIs) that are designated as AEs of special interest will be summarized in separate tables from other AEs. Any AE of unknown etiology associated with MK-3475 exposure will be evaluated to determine if it is possibly an event of clinical interest (ECI) of a potentially immunologic etiology (irECI).

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.

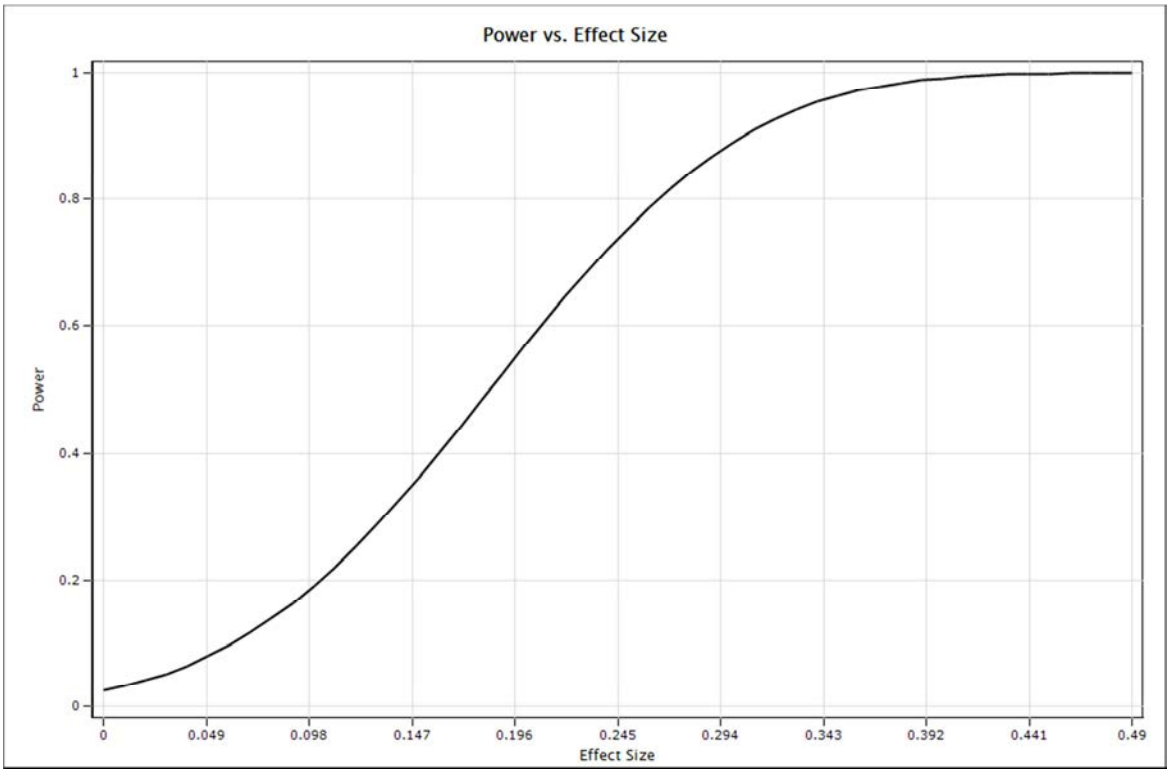

Figure 2 Power for primary hypothesis under different effect size assumptions

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 12.

Table 12 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 12 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 12 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 Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice: Consolidated Guideline and other generally accepted standards of good clinical practice); and all applicable federal, state and local laws, rules and regulations relating to the conduct of the clinical trial.

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

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

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

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

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

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

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

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

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

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

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

10.4 Compliance with Trial Registration and Results Posting Requirements

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

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

10.5 Quality Management System

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

10.6 Data Management

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

Detailed information regarding Data Management procedures for this protocol will be provided by the Sponsor.

10.7 Publications

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

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

the efficacy and safety measures, the statistical analysis plan, and any amendments relating to those sections. The Sponsor reserves the right to redact proprietary information.

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

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

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

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