Official Protocol Title:	An Open-label, Randomized Phase I Study Investigating Safety, Tolerability, Pharmacokinetics, and Efficacy of Pembrolizumab (MK-3475) in Chinese Subjects with Non-Small-Cell Lung Cancer
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TITLE:

An Open-label, Randomized Phase I Study Investigating Safety, Tolerability, Pharmacokinetics, and Efficacy of Pembrolizumab (MK-3475) in Chinese Subjects with Non-Small-Cell Lung Cancer

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DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
3475-032-03	17-DEC-2020	Added standard extension study language
3475-032-02	25-JAN-2017	Changes made to inclusion, exclusion criteria, trial flow chart, and discontinuation criteria to make the protocol clearer and align with the latest safety information of pembrolizumab
3475-032-01	04-APR-2016	Changes made to remove language and sections related to the sample collection of Planned Genetic Analysis (PGA) and Future Biomedical Research (FBR) per China agency's feedback
3475-032-00	01-MAR-2016	Original protocol

SUMMARY OF CHANGES

PRIMARY REASON(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
1.0	Trial Summary/Duration of Participation	Added: Once the subject has achieved the study objective or the study has ended, the subject is discontinued from the study and may be enrolled in an extension study to continue protocol defined assessments and treatment.	To include extension study
2.2	Trial Diagram	Added: Study Completion and Pembrolizumab Extension Study	
5.10	Beginning and End of the Trial	Added: Upon study completion, participants are discontinued and may be enrolled in a pembrolizumab extension study, if available.	

1.0 TRIAL SUMMARY

Abbreviated Title	Phase I Study Investigating Safety, Tolerability, Pharmacokinetics, and Efficacy of Pembrolizumab (MK-3475) in Chinese subject with Non-Small-Cell Lung Cancer
Trial Phase	I
Clinical Indication	Locally advanced or metastatic non-small cell lung cancer (NSCLC)
Trial Type	Interventional
Type of control	No Treatment Control
Route of administration	Intravenous
Trial Blinding	Unblinded Open-label
Treatment Groups	Pembrolizumab: 2 mg/kg administered every 3 weeks (Q3W), 10 mg/kg Q3W, or 200 mg fixed dose Q3W
Number of trial subjects	Approximately 42 subjects will be enrolled.
Estimated duration of trial	The Sponsor estimates that the trial will require approximately 2.5 years from the time the first subject signs the informed consent until the last subject's last study-related phone call or visit.
Duration of Participation	Each subject will participate in the trial for up to 2 years from the time the subject signs the Informed Consent Form (ICF) through the final contact. For PK analysis, the dosing interval in the first treatment cycle will be 28 days, followed by Q3W intervals. After PK evaluation, subjects will continue their allocated dose until 35 cycles of therapy have been administered, documented disease progression, unacceptable adverse event(s), intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw the subject, subject withdraws consent, pregnancy of the subject, noncompliance with trial treatment or procedure requirements, or administrative reasons; or attaining an investigator-determined confirmed CR that have been treated for at least 8 cycles (approximately 24 weeks) with Pembrolizumab, and has at least two treatments with Pembrolizumab beyond the date when the initial CR was declared. Subjects dropping out from PK assessment can still continue the study for safety and efficacy evaluation. Once the subject has achieved the study objective or the study has ended, the subject is discontinued from the study and may be enrolled in an extension study to continue protocol-defined assessments and treatment.
Randomization Ratio	1:1:1

2.0 TRIAL DESIGN

2.1 Trial Design

This is an open-label, randomized, phase I study of intravenous (IV) Pembrolizumab to investigating the safety, tolerability, pharmacokinetics (PK), and efficacy of Pembrolizumab in Chinese adult subjects with locally advanced or metastatic non-small-cell lung cancer.

Approximately 42 subjects will be randomized to 2 mg/kg Q3W, 10 mg/kg Q3W and 200 mg fixed dose Q3W of Pembrolizumab in a ratio of 1:1:1, and stratified by gender. Assignment of different dose levels will be unblinded. The investigator will know the treatment administered but not the treatment allocation schedule given randomization will occur centrally. For PK analysis, the dosing interval in the first treatment cycle will be 28 days, followed by Q3W intervals. After PK evaluation, subjects will continue their allocated dose until 35 cycles of therapy have been administered, documented disease progression, unacceptable adverse event(s), intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw the subject, subject withdraws consent, pregnancy of the subject, noncompliance with trial treatment or procedure requirements, or administrative reasons. Subjects dropping out from PK assessment can still continue the study for safety and efficacy evaluation.

The primary objective is to evaluate the tolerability and safety profile of Pembrolizumab in Chinese subjects with NSCLC. Adverse events (AEs) across all dose groups 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. Antibody against Pembrolizumab and its impact on plasma concentration of Pembrolizumab will also be monitored in the study.

Another primary objective is to evaluate the PK profile of Pembrolizumab in Chinese adult subjects with NSCLC. PK samples following a single dose will be collected at multiple time points at the first treatment cycle up to 28 days. Then pre-dose samples will be collected at cycle 1, 2, 4, 6, and 8, and every 4 cycles thereafter. Additional blood sample will be drawn at cycle 8 at multiple time points for PK profile assessment at steady state. Single dose parameters (i.e., $AUC_{0\text{-}28days}$, C_{max}, T_{max}, and $t_{1/2}$, etc.) and multiple dose parameters (i.e., C_{trough}, $AUC_{0\text{-}21day}$, and C_{max} at steady state) will be evaluated among Chinese subjects.

The secondary objective of the study is to evaluate anti-tumor activity of Pembrolizumab in Chinese adult subjects with NSCLC. Subjects will be evaluated every 9 weeks (63 ± 7 days) with radiographic imaging to assess response to treatment. All images obtained on study will be submitted for central radiologists' review; they will assess the images using Response Evaluation Criteria In Solid Tumors 1.1 (RECIST 1.1) and immune-related RECIST (irRECIST, details are provided in the Site Imaging Manual) for determination of Objective Response Rate (ORR) and Progression-Free Survival (PFS). Overall survival (OS) and duration of response (DOR) will also serve as supportive efficacy endpoints.

After the end of treatment, each subject will be followed for a minimum of 30 days for adverse event monitoring (serious adverse events (SAE) will be collected for up to 90 days after the end of treatment). Subjects will have post-treatment follow-up for disease status, including initiating a non-study cancer treatment and experiencing disease progression, until

death, withdrawing consent, becoming lost to follow-up, or the end of the study. See Figure 1 for study 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.

2.2 Trial Diagram

The trial design is depicted in Figure 1 below.

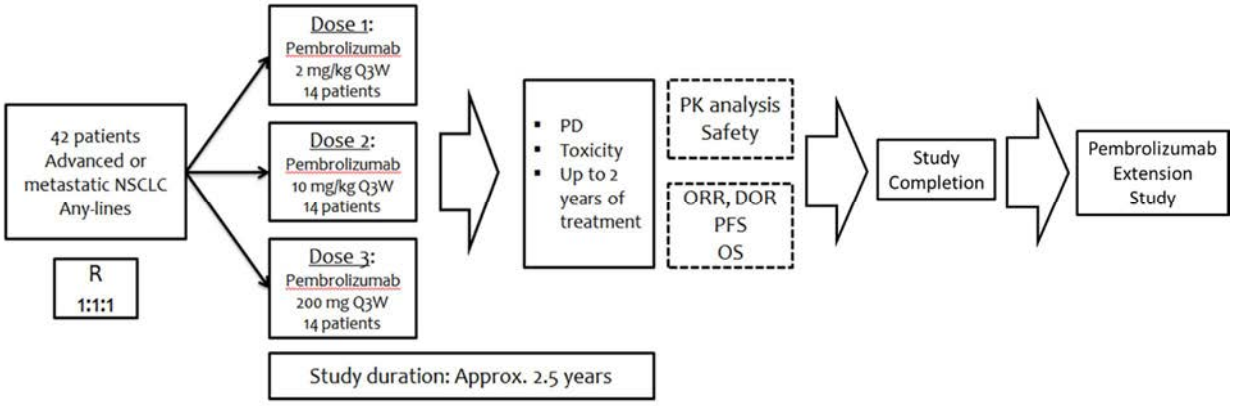

Figure 1 Trial Design

Note: NSCLC = non-small-cell lung cancer; R = randomization; Q3W = every 3 weeks; PD = disease progression; PK = pharmacokinetic; ORR = objective response rate; DOR = duration of response; PFS = progression-free survival; OS = overall survival

3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

3.1 Primary Objective(s) & Hypothesis(es)

In Chinese adult subjects with locally advanced or metastatic NSCLC:

1) **Objective:** To evaluate the tolerability and safety profile of Pembrolizumab by dose regimen (2 mg/kg Q3W, 10 mg/kg Q3W, and 200 mg fixed dose Q3W).
2) **Objective:** To evaluate the pharmacokinetic (PK) profile of Pembrolizumab by dose regimen.

3.2 Secondary Objective(s) & Hypothesis(es)

1) **Objective**: To evaluate the objective response rate (ORR), the duration of response (DOR) and progression-free survival (PFS) per RECIST 1.1 and irRECIST by central radiologists' review, and overall survival (OS) of Pembrolizumab by dose regimen, in Chinese adult subjects with locally advanced or metastatic NSCLC.

4.0 BACKGROUND & RATIONALE

4.1 Background

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

4.1.1 Pharmaceutical and Therapeutic Background

The programmed cell death 1 (PD-1) pathway represents a major immune control switch which may be engaged by tumor cells to overcome active T-cell immune surveillance. The normal function of PD -1, expressed on the cell surface of activated T cells under healthy conditions, is to down modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 is an Ig superfamily member which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) [1, 2]. Although healthy organs express low level, the ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in various tumors. High expression of PD-L1 on tumor cells (and to a lesser extent of PD-L2) has been found to correlate with poor prognosis and survival in various cancer types, including renal cell carcinoma (RCC), pancreatic carcinoma [3], hepatocellular carcinoma [4], ovarian carcinoma [5] and NSCLC [6]. Furthermore, PD-1 has been suggested to regulate tumor-specific T-cell expansion in subjects with malignant melanoma.

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

Monoclonal antibodies (mAb) against PD-1 such as Nivolumab (BMS-936558, MDX-1106) have been tested in multiple human solid tumors and promising clinical activity was noted in melanoma, RCC, and NSCLC at multiple doses up to 10 mg/kg Q2W [7]. Nivolumab was also well tolerated up to the dose of 20 mg/kg in phase I study in Japanese subjects with advanced solid tumors, and showed anti-tumor activities in melanoma, colorectal cancer (CRC), and thyroid carcinoma [8].

Pembrolizumab (MK-3475) is a potent and highly selective humanized anti-PD-1 mAb of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands PD-L1 and PD-L2. This blockade enhances functional activity of the target lymphocytes to facilitate tumor regression and ultimately immune rejection. Therapeutic studies in mouse models have shown that administration of antibodies blocking PD-1/PD-L1 interaction enhances infiltration of tumor-specific CD8+ T-cells and leads ultimately to tumor rejection, either as a mono-therapy or in combination with other treatment modalities. See the Investigator Brochure for detailed information.

Lung cancer is the most commonly diagnosed cancer and the leading cause of cancer death worldwide including China. Non-small cell lung cancer (NSCLC) accounts for approximately 85% of all lung cancers; of those, approximately 40%-60% have adenocarcinoma histology; 10%-15%, squamous histology; 5%, neuroendocrine histology; and the rest, "not otherwise specified" [9, 10]. The mortality of NSCLC is much higher in China than in US and Europe. In China, age-standardized incidence rate is 33.5 per 100,000 persons, with an estimated number of 653,000 subjects per year. The age-standardized

mortality rate is 32.5 per 100,000 persons, with an estimated number of 597,000 subjects per year. The incidence and mortality of lung cancer in China would gradually increase in the next 20 years, attributing to cigarette smoking and air pollution. Advances in the treatment of subjects with NSCLC are badly needed.

4.1.2 Ongoing Clinical Trials

An open-label Phase I trial (Protocol 001) is being conducted to evaluate the safety and clinical activity of single agent MK-3475. The dose escalation portion of this trial evaluated three dose levels, 1 mg/kg, 3 mg/kg, and 10 mg/kg, administered every 2 weeks (Q2W), in subjects with advanced solid tumors. All three dose levels were well tolerated and no dose limiting toxicities were observed. Based on PK data showing a half-life of 21 days, the protocol was amended to change the dosing frequency in the expansion cohort to every 3 weeks (Q3W). Two subjects with MEL from the initial cohort of subjects treated in Protocol 001 showed confirmed objective responses based on RECIST 1.1. The ongoing expansion cohort in Protocol 001 is enrolling MEL subjects and promising preliminary anti-cancer activity has been observed (50/135 [37%; 95% CI 29%, 45%] objective responses (confirmed) by irRECIST per investigators' review; 52/117 [44%; 95% CI 35%, 54%] best objective response by RECIST 1.1 (confirmed and unconfirmed) per independent radiologists' review). Of further note, those patients with melanoma who were treated with MK-3475 10 mg/kg Q2W had a best objective response rate of 29/52 [56%; 95% CI 41%, 69%] by RECIST 1.1 (confirmed and unconfirmed) per independent radiologists' review (32/57 [56%; 95% CI 42%, 69%] by irRECIST (confirmed) per investigators' review), and those treated at 10 mg/kg Q3W had a best objective response rate of 16/45 [36%; 95% CI 22%, 51%] by RECIST 1.1 (confirmed and unconfirmed) per independent radiologists' review (15/56 [27%; 95% CI 16%, 40%] by irRECIST (confirmed) per investigators' review). None of these patients were randomized between the two treatment schedules. Amongst approximately 130 subjects with MEL treated with MK-3475 at Q2W and Q3W the most common AEs were fatigue, nausea, rash, diarrhea, cough, pruritus, arthralgia, headache, abdominal pain, increased AST, pyrexia, and decreased appetite. The most common drug-related AEs included fatigue, rash, pruritus, diarrhea, and arthralgia. The incidence of Grade 3-5 AEs was 27%. Potentially immune-related AEs have been observed, including pneumonitis in both the melanoma and NSCLC cohorts. Although most cases do not result in death, in one instance, a 96-year old man with melanoma who experienced Grade 2 pneumonia/pneumonitis suffered a fatal myocardial infarction while being treated for the pneumonia/pneumonitis.

MK-3475 Protocol 001 (PN001) Part C enrolled 38 subjects with NSCLC who experienced progression of cancer after initiation of their second line of systemic therapy to receive monotherapy MK-3475. The best overall response rate was 24% by investigator assessed irRECIST, and 21% by independently assessed RECIST v1.1. Clinical responses have been observed in subjects with adenocarcinoma, squamous cell carcinoma, and large cell carcinoma when assessed by irRECIST. The median duration of treatment amongst responders has not yet been reached, but the follow-up is a minimum of 62 weeks. Most responders continue on therapy.

Subjects were required to submit a newly obtained tumor biopsy prior to initiating therapy with MK-3475 to evaluate the tumors for expression of PD-L1, the presumptive predictive

biomarker of MK-3475, using an immunohistochemistry assay. After observing that patients who expressed higher levels of PD-L1 by the IHC assay were more likely to respond, more patients with NSCLC enrolled on MK-3475 PN001 Part F. Most of these patients expressed PD-L1 on the tumor cell membrane. The Sponsor remained blinded to the quantitative PD-L1 score.

146 patients in this training set had at least 19 weeks of follow-up; their quantitative tumoral PD-L1 results were matched to their best overall response by investigator assessed irRECIST and by independently assessed RECIST v1.1. The relationship between tumor PD-L1 expression and best overall response was assessed by logistic regression analysis, with a statistically significant association identified (p-value irRECIST <0.0001, RECIST <0.001). The relationship between tumor PD-L1 expression and PFS and OS were assessed by Cox regression analysis, with a statistically significant association identified (p-value PFS <0.001, OS 0.012).

Several means of quantitatively scoring PD-L1 expression were evaluated using ROC curve analyses and assessment of positive and negative predictive values of potential strongly /weakly positive cutoffs. Based on these analyses, a proportion score with a cutoff of 50% or more of tumor cells staining for PD-L1 was selected as an optimal strongly /weakly positive cutoff. The best overall response rate of patients with strongly positive tumors in the training set by investigator-assessed irRECIST was 46% (95% CI: 30%, 61%) compared to 8% (95% CI: 3%, 15%) in patients with weakly positive (1-49% positive)/negative tumors. The best overall response rate of patients with strongly positive tumors in the training set by independently-assessed RECIST was 37% (95% CI: 22%, 53%) compared to 11% (95% CI: 6%, 20%) in patients with 1-49% positive/negative tumors.

Additionally, it was observed in a retrospective epidemiology study that patients who had surgical specimens from definitive resections, and another surgical resection specimen or a core needle biopsy at the time of relapse do not maintain the same degree of expression of PD-L1. The correlation among samples from two time points when the categories are strongly positive, 1-49% positive and negative is suboptimal at 55%. The later specimen could be any of the other categories. Therefore, to minimize any potential risk that using archival tumor samples may pose for stratifying patients and identifying the primary analysis set, new tumor biopsies will be required.

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

The ongoing global phase I study has demonstrated acceptable tolerability of Pembrolizumab in subjects with various solid tumors including NSCLC. The promising anti-tumor activities of Pembrolizumab in melanoma and NSCLC have been indicated in the expansion studies of PN001 and entered phase III program.

This is the first clinical study of Pembrolizumab in Chinese subjects with solid tumors. The safety, tolerability, and preliminary anti-tumor activity of Pembrolizumab will be evaluated in Chinese adult subjects with NSCLC. The study design is consistent with typical design for oncological drugs to meet its objectives. Considering its primary objectives, open label,

randomized design was adequate. In addition, the available safety information supports the parallel design.

4.2.2 Rationale for Dose Selection/Regimen/Modification

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

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

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

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

The choice of the 200 mg Q3W as an appropriate dose for the switch to fixed dosing is based on simulations performed using the population PK model of Pembrolizumab showing that the

fixed dose of 200 mg every 3 weeks will provide exposures that 1) are optimally consistent with those obtained with the 2 mg/kg dose every 3 weeks, 2) will maintain individual patient exposures in the exposure range established in melanoma as associated with maximal efficacy response and 3) will maintain individual patients exposure in the exposure range established in melanoma that are well tolerated and safe.

A fixed dose regimen will simplify the dosing regimen to be more convenient for physicians and to reduce potential for dosing errors. A fixed dosing scheme will also reduce complexity in the logistical chain at treatment facilities and reduce wastage.

Therefore, in this China phase I study, we will investigate the safety, PK and preliminary efficacy of 2 mg/kg Q3W, 10 mg/kg Q3W, and 200 mg fixed dose Q3W among Chinese subjects with NSCLC; and no difference is expected for safety, efficacy, or PK parameters among the 3 dose groups included in this study.

4.2.3 Rationale for Endpoints

4.2.3.1 Rationale for Safety Monitoring Indicators

Adverse events will be graded and recorded throughout the study according to NCI CTCAE, version 4.0. Adverse Events (AEs) will be analyzed including but not limited to all AEs, SAEs, fatal AEs, and laboratory changes. Because of the feature of immunotherapy of Pembrolizumab, special attention will be given to immune-related adverse events (e.g., gut, skin, liver, endocrine organs, others) including immune laboratory tests. Because it is the first study of Pembrolizumab in Chinese patients, antibody against Pembrolizumab and its impact on plasma concentration of Pembrolizumab will also be monitored in the study.

4.2.3.2 Rationale for PK Estimation

Preclinical and clinical studies have demonstrated the half-life of Pembrolizumab is around 14 to 21 days after the administration. Because it is the first study of Pembrolizumab in Chinese patients, PK parameters (e.g., $AUC_{0\text{-}28day}$, C_{max}, T_{max}, $t_{1/2}$) will be collected up to 28 days at cycle 1 to estimate the PK profiles following single dose administration. Multiple dose PK parameters (e.g., C_{trough}, $AUC_{0\text{-}21day}$ and C_{max} at steady state) will be also explored. Single-dose $AUC_{0\text{-}28day}$ and multiple-dose $AUC_{0\text{-}21day}$ are primary parameters of PK evaluation because AUC is the most comprehensive measurement for exposure.

4.2.3.3 Efficacy Endpoints

The anti-tumor activity will be evaluated as an efficacy endpoints based on radiographic (CT or MRI), and tumor markers evaluations. The Response Evaluation Criteria in Solid Tumors (RECIST 1.1) and immune-related RECIST (irRECIST) will be applied for evaluation of tumor response.

The secondary objective is to evaluate ORR, DOR, PFS per RECIST 1.1 and irRECIST, and OS.

RECIST 1.1 will be used to determine the dates of progression as this methodology is accepted by regulatory authorities. Images read by central radiologists blinded to treatment

assignment can minimize bias in the response assessments. In addition, final determination of radiologic progression will be based on the central assessment of progression, rather than site assessment. Real-time determination of radiologic progression as determined by central review (verification of progression) will be communicated to the site.

4.2.3.4 Immune-related RECIST

RECIST 1.1 will be adapted to account for the unique tumor response characteristics seen with treatment of pembrolizumab. Immunotherapeutic agents such as pembrolizumab may produce antitumor effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents, and can manifest a clinical response after an initial increase in tumor burden or even the appearance of new lesions. Standard RECIST may not provide an accurate response assessment of immunotherapeutic agents such as pembrolizumab. Therefore, RECIST 1.1 will be used with the following adaptations:

If radiologic imaging by central imaging vendor verifies initial progression (PD), tumor assessment should be repeated ≥4 weeks later in order to confirm PD with the option of continuing treatment per below while awaiting radiologic confirmation of progression. If repeat imaging shows < 20% tumor burden compared to nadir, stable or improved previous new lesion (if identified as cause for initial PD), and stable/improved non-target disease (if identified as cause for initial PD), treatment may be continued / resumed. If repeat imaging confirms PD due to any of the scenarios list below, subjects will be discontinued from study therapy (exception noted in Section 7.1.2.6.3). In determining whether or not the tumor burden has increased or decreased, investigators should consider all target lesions as well as non-target lesions (please refer to the Procedure Manual).

Scenarios where PD is confirmed at repeat imaging:

- Tumor burden remains ≥20% and at least 5 mm absolute increase compared to nadir
- Non-target disease resulting in initial PD is worse (qualitative)
- New lesion resulting in initial PD is worse (qualitative)
- Additional new lesion(s) since last evaluation

In subjects who have initial evidence of radiological PD verified by central imaging vendor, it is at the discretion of the treating physician whether to continue a subject on study treatment until repeat imaging is obtained. This clinical judgment decision should be based on the subject's overall clinical condition, including performance status, clinical symptoms, and laboratory data. Subjects may receive pembrolizumab treatment while waiting for confirmation of PD if they are clinically stable as defined by the following criteria:

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

When feasible, subjects should not be discontinued until progression is confirmed. This allowance to continue treatment despite initial radiologic progression takes into account the observation that some subjects can have a transient tumor flare in the first few months after the start of immunotherapy, but with subsequent disease response. Subjects that are deemed clinically unstable are not required to have repeat imaging for confirmation of progressive disease.

4.3 Benefit/Risk

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

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

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

Chinese Male/Female subjects with locally advanced or metastatic NSCLC of at least 18 years of age will be enrolled in this trial.

5.1.2 Subject Inclusion Criteria

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

1. Be of the Chinese race, i.e. Chinese descent born in China, and have a Chinese home address.
2. Be willing and able to provide written informed consent/assent for the trial.
3. Age ≥18 years on day of signing informed consent.
4. Have a life expectancy of at least 3 months.
5. Have histologically /cytological confirmed, advanced unresectable NSCLC and have measurable disease based on RECIST 1.1 as determined by the site. Tumor lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions.
6. Have failed established standard medical anti-cancer therapies or have been intolerant to such therapy, or in the opinion of the investigator have been considered ineligible for any form of standard therapy on medical grounds.
7. Have a performance status of 0 or 1 on the Eastern Cooperative Oncology Group Performance Status (ECOG P.S.) within 3 days prior to the first dose of study therapy.

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

Table 1 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1,500 /mcL (without supportive care)
Platelets	≥100,000 / mcL
Hemoglobin	≥9 g/dL or ≥5.6 mmol/L (without erythropoietin dependency and without transfusion within last 2 weeks)
Renal	
Serum creatinine **OR** Measured or calculated[a] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5xULN **OR** ≥60 mL/min for subject with creatinine levels >1.5x institutional ULN
Hepatic	
Serum total bilirubin	≤1.5xULN **OR** Direct bilirubin ≤ULN for subjects with total bilirubin levels >1.5xULN
AST (SGOT) and ALT (SGPT)	≤2.5xULN **OR** ≤5xULN for subjects with liver metastases
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT) Activated Partial Thromboplastin Time (aPTT)	≤1.5xULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants ≤1.5xULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
[a] Creatinine clearance should be calculated per institutional standard. If no local guideline is available, Creatinine Clearance should be calculated using the Cockcroft-Gault Method: CrCl = [(140-age) * weight (kg) * (0.85 for females only)] / (72 * serum creatinine)	

9. Female subject of childbearing potential must have a negative urine or serum pregnancy test within 72 hours prior to receiving the first dose of trial 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 must be willing to use an adequate method of contraception as outlined in Section 5.7.2 - Contraception, for the course of the trial through 120 days after the last dose of trial drug. Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject.
11. Male subjects of child-bearing potential must agree to use an adequate method of contraception as outlined in Section 5.7.2 - Contraception, starting with the first dose of trial therapy through 120 days after the last dose of trial therapy. Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject.

5.1.3 Subject Exclusion Criteria

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

1. Has had chemotherapy, radioactive, or biological cancer therapy within 4 weeks prior to the first dose of study therapy Pembrolizumab, or who has not recovered to CTCAE grade 1 or better from the adverse events due to cancer therapeutics administered more than 4 weeks earlier.
2. Is currently participating and receiving study therapy or has participated in a study of an investigational agent and receive study therapy or used an investigational device within 4 weeks of the first dose of trial treatment

   Note: Subjects who have entered the follow-up phase of an investigational study may participate as long as it has been 4 weeks since the last dose of the previous investigational agent or device.
3. Is expected to require any other form of antineoplastic therapy while on study (including maintenance therapy with another agent for NSCLC).
4. Has a medical condition that requires chronic systemic steroid therapy or on any other form of immunosuppressive medication.
5. Has a known history of a hematologic malignancy, primary brain tumor or sarcoma, or of another primary solid tumor, unless the subject has undergone potentially curative therapy with no evidence of that disease for 5 years.
   - Note: The time requirement for no evidence of disease for 5 years does not apply to the 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.
6. Has known central nervous system (CNS) metastases and/or carcinomatous meningitis.
   Note: Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least 4 weeks prior to the first dose of trial treatment and neurologically asymptomatic), have no evidence of new or enlarging brain metastases confirmed by repeat imaging, and have not required steroids for at least 14 days before first dose of trial treatment.
7. Has a history of (non-infectious) pneumonitis that required steroids or has current pneumonitis
8. Has active autoimmune disease that has required systemic treatment in past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.
9. Had prior treatment targeting PD-1: PD-L1 axis or CTLA, or was previously randomized in any Pembrolizumab trial.

- Examples of such agents include (but are not limited to): Nivolumab (BMS936558 MDX-1106 or ONO-4538); Pidilizumab (CT011); AMP-224; BMS-936559 (MDX 1105); MPDL3280A (RG7446); and MEDI4736.

10. Has an active infection requiring systematic therapy.
11. Is positive for Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies is detected.
12. 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.
    - Note: testing for HCV RNA (quantitative), HBsAg will be performed at screening; if results obtained within 3 months before screening are available, they can be used.
13. 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.
14. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.
15. Has received or will receive a live vaccine within 30 days prior to the first administration of study medication.
16. 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).
17. Female subject is pregnant or breastfeeding, or expecting to conceive or male subject expected to father child within the projected duration of the trial, starting with the screening visit (Visit 1) through 120 days after the last dose of Pembrolizumab.

5.2 Trial Treatment(s)

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

Table 2 Trial Treatment

Drug	Dose/ Potency	Dose Frequency	Route of Administration	Regimen/ Treatment Period	Use
Pembrolizumab (n=14)	2 mg/kg	Q3W (Cycle 1: 28 days)	IV infusion	Day 1 of each cycle	Experimental
Pembrolizumab (n=14)	10 mg/kg	Q3W (Cycle 1: 28 days)	IV infusion	Day 1 of each cycle	Experimental
Pembrolizumab (n=14)	200 mg fixed dose	Q3W (Cycle 1: 28 days)	IV infusion	Day 1 of each cycle	Experimental
All subjects will receive multiple cycle treatment of the Pembrolizumab for 35 cycles until subjects withdraw or discontinuation for reasons defined in the protocol.					

All supplies indicated in Table 2 above will be provided centrally by the Sponsor.

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

5.2.1 Dose Selection/Modification

5.2.1.1 Dose Selection (Preparation)

The rationale for selection of doses to be used in this trial is provided in Section 4.0 – Background and Rationale. For 2 mg/kg and 10 mg/kg arms, the dose amount required to prepare the MK-3475 infusion solution will be based on the subject's weight in kilograms (kg). Details on the dose calculation, preparation and administration are provided in the Procedures Manual.

5.2.1.2 Dose Modification (Escalation/Titration/Other)

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

Table 3 Dose Modification Guidelines for Drug-Related Adverse Events

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 (see exception below)[1]	Permanently discontinue
Type 1 diabetes mellitus (if new onset) or Hyperglycemia	T1DM or 3-4	Hold pembrolizumab for new onset Type 1 diabetes mellitus or Grade 3-4 hyperglycemia associated with evidence of beta cell failure.	Resume pembrolizumab when patients are clinically and metabolically stable.
Hypophysitis	2-4	Toxicity resolves to Grade 0-1. Therapy with pembrolizumab can be continued while endocrine replacement therapy is instituted	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
Hyperthyroidism	3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue
Hypothyroidism		Therapy with pembrolizumab can be continued while thyroid replacement therapy is instituted	Therapy with pembrolizumab can be continued while thyroid replacement therapy is instituted.
Infusion Reaction	2[2]	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 or recurrent 2	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[3]	3 or Severe	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue

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

[1] For patients with liver metastasis who begin treatment with Grade 2 AST or ALT, if AST or ALT increases by greater than or equal to 50% relative to baseline and lasts for at least 1 week then patients should be discontinued.

[2] If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose; Refer to Table 4 – Infusion Reaction Treatment Guidelines for further management details.

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

Dosing interruptions are permitted in the case of medical / surgical events or logistical reasons not related to study therapy (e.g., elective surgery, unrelated medical events, patient vacation, and/or holidays). Subjects should be placed back on study therapy within 3 weeks

of the scheduled interruption, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the patient's study record.

5.2.2 Timing of Dose Administration

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

Pembrolizumab 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).

5.2.3 Trial Blinding/Masking

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

5.3 Randomization or Treatment Allocation

Treatment allocation/randomization will occur centrally using an interactive voice response system / integrated web response system (IVRS/IWRS). There are 3 treatment arms. Subjects will be assigned randomly in a 1:1:1 ratio to 2 mg/kg Q3W, 10 mg/kg Q3W, and 200 mg fixed dose Q3W of Pembrolizumab, respectively.

5.4 Stratification

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

1. Gender (male vs. female)

5.5 Concomitant Medications/Vaccinations (Allowed & Prohibited)

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

5.5.1 Allowed Concomitant Medications

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

All concomitant medications received within 4 weeks before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered within 90 days after the last dose of trial treatment should be recorded for SAEs and ECIs as defined in Section 7.2.

5.5.2 Prohibited Concomitant Medication

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

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab
- Radiation therapy
  - Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed after consultation with Sponsor.
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid (oral) vaccine. The killed virus vaccines used for seasonal influenza vaccines for injection are allowed; however live attenuated intranasal influenza vaccines (e.g. Flu - Mist®) are not allowed.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor (e.g., for control of acute asthma symptoms).

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; however, subjects must be discontinued from the safety follow-up phase if they begin a non-trial treatment.

5.6 Rescue Medications & Supportive Care

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of adverse events with potential immunologic etiology are outlined below. Where appropriate, these guidelines include the use of oral or intravenous treatment with corticosteroids as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms

may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to Pembrolizumab.

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

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

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

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

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

  Table 4 below shows treatment guidelines for subjects who experience an infusion reaction associated with administration of Pembrolizumab.

Table 4 Infusion Reaction Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 hrs	**Stop Infusion and monitor symptoms.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. **Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.**	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab 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

Pembrolizumab may have adverse effects on a fetus in utero. Furthermore, it is not known if Pembrolizumab 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 meet 1 of the following criteria:

- She is postmenopausal, defined as at least 12 months with no menses without an alternative medical cause. In women <45 years of age who are not using hormonal contraception or hormonal replacement therapy, a high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state. In the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
- She had a hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy or bilateral tubal ligation/occlusion, at least 6 weeks prior to screening.
- She has a congenital or an acquired condition that prevents childbearing.

Female and male subjects of reproductive potential must agree to avoid becoming pregnant or impregnating a partner, respectively, while receiving trial drug and for 120 days after the last dose of trial drug by complying with 1 of the following:

- Practice abstinence from heterosexual activity.

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

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

Acceptable methods of contraception are[‡]:

- Single method (1 of the following is acceptable):
    - Intrauterine device (IUD)
    - Vasectomy of a female subject's male partner
    - Contraceptive rod implanted into the skin
- Combination method (requires use of 2 of the following):
    - Diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide)
    - Cervical cap with spermicide (nulliparous women only)

- Contraceptive sponge (nulliparous women only)
- Male condom or female condom (cannot be used together)
- Hormonal contraceptive: oral contraceptive pill (estrogen/progestin pill or progestin-only pill), contraceptive skin patch, vaginal contraceptive ring, or subcutaneous contraceptive injection

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

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

5.7.3 Use in Pregnancy

If a female subject inadvertently becomes pregnant while on treatment with Pembrolizumab, 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 Pembrolizumab 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 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 may continue to be monitored in the trial, as long as the subject does not withdraw consent) for any of the following reasons:

- Radiographic disease progression
    - Note: A subject may be granted an exception to continue on treatment with confirmed radiographic progression if clinically stable or clinically improved, please see Section 7.1.2.6.2.1
- Unacceptable adverse experiences as described in Section 5.2.1.2.
- Any progression or recurrence of any malignancy, or any occurrence of another malignancy that requires active treatment
- Intercurrent illness that prevents further administration of treatment
- Recurrent Grade 2 pneumonitis
- Completed 35 cycles treatment (approximately 2 years) with pembrolizumab
    - Note: 35 cycles of study medication is calculated from the date of first dose. Subjects who stop pembrolizumab after 35 cycles (approximately 2 years) may be eligible for up to 17 cycles (approximately 1 year) of additional study treatment if they progress after stopping study treatment provided they meet the requirements detailed in Section 7.1.5.2.1. Subjects may be retreated in the Second Course Phase (Retreatment) for up to an additional 17 cycles (approximately 1 year).
- 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

5.8.1 Discontinuation of Study Therapy after CR

If a Pembrolizumab treated subject attains an investigator-determined confirmed CR that have been treated for at least 8 cycles (approximately 24 weeks) with Pembrolizumab, and has at least two treatments with Pembrolizumab beyond the date when the initial CR was declared, investigator may consider stopping therapy with Pembrolizumab. Subjects who discontinue Pembrolizumab after attaining a CR and then experience radiographic disease progression may be eligible for up to 17 cycles (approximately 1 year) of re-treatment with Pembrolizumab at the discretion of the investigator if the subject meets the safety parameters listed in the Inclusion/Exclusion criteria. The subject will resume therapy at the same dose and schedule at the time of initial discontinuation.

5.9 Subject Replacement Strategy

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

5.10 Beginning and End of the Trial

The overall study begins when the first participant (or their legally acceptable representative) provides documented informed consent. The overall study ends when the last participant completes the last study-related contact, withdraws consent, or is lost to follow-up (ie, the participant is unable to be contacted by the investigator).

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

5.11 Clinical Criteria for Early Trial Termination

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

6.0 TRIAL FLOW CHART

6.1 Treatment Phase

	Screening[1]	Cycle 1									Cycle 2 and Additional Cycles	End of Treatment	Safety Follow-up[2]	Follow-up Visits[21]
Scheduling Window	-28 to -1 Days	1 to 28 Days									Every 21 Days		30 Days ± 3 Days after last dose	
Cycle Day		1	2	3	5	8	15	22	25	28[3]	1 (±3)			
Administrative Procedures														
Informed Consent[4]	X													
Inclusion/Exclusion Criteria	X													
Demographics, Medical History	X													
Current NSCLC Disease Details and Prior Treatment[5]	X													
Prior Medications and Concomitant Medications[5]	X											X		
Clinical Procedures / Assessments														
Vital Signs/Weight[6]	X	X				X	X	X			X	X	X	
Full Physical Examination	X											X		
Directed Physical Examination		X									X			
ECOG Performance Status	X										X	X	X	
12-Lead ECG	X													
Review Adverse Events[7]	X----------X													
Review Concomitant Medications	X----------X													

	Screening[1]	Cycle 1									Cycle 2 and Additional Cycles	End of Treatment	Safety Follow-up[2]	Follow-up Visits[21]
Scheduling Window	-28 to -1 Days	1 to 28 Days									Every 21 Days		30 Days ± 3 Days after last dose	
Cycle Day		1	2	3	5	8	15	22	25	28[3]	1			
Laboratory Procedures / Assessments														
CBC with Differential[8]	X										X	X	X	
Comprehensive Serum Chemistry Panel[8]	X						X				X		X	
Coagulation Parameters[9]	X												X	
Urinalysis[1]	X												X	
Pregnancy Test - Urine or Serum HCG[10]	X													
Thyroid Function[11]	X										X		X	
Anti-Pembrolizumab Antibodies[12]		X									X		X	
Pharmacokinetics[13]		X	X	X		X	X	X			X		X	X
HIV, Hepatitis B and C[14]	X													
EGFR Mutation / ALK Translocation status[15]	X													
Efficacy Measurements														
Tumor Imaging	X[16]										X[17]	X[18,19]		X[19]
Drug Administration														
Study Drug Administration[20]		X									X			

1. Routine laboratory tests (serum chemistry; hematology; urinalysis) for screening should be performed within 10 days of enrollment. ECOG PS should be assessed within 3 days prior to the first dose of trial treatment.
2. The mandatory Safety Follow-Up visit should be conducted 30 days (±3 days) after the last dose of study therapy (serious adverse events will be collected for up to 90 days after the end of treatment) or before the initiation of a new treatment, whichever comes first. Subjects who are discontinued from the study due to an unacceptable drug-related adverse event will be followed until the resolution of the adverse event (AE) to Grade 0-1 or stabilization or until beginning of a new therapy for their cancer, whichever occurs first.

3. Day 28 = pre-dose for Cycle 2/Day 1 for subjects continuing in the study.
4. Written consent must be obtained prior to performing any protocol specific procedure. Results of a test performed as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame (e.g. within 28 days prior to Cycle 1, Day 1). Assign Baseline number when the study informed consent is signed.
5. Includes history of treatment for the primary diagnosis, including prior systemic, radiation treatment and surgical treatment. Date of last prior cancer treatment must be documented. Radiographic studies performed prior to study entry may be collected for review by the investigator. Report complete medication history for 4 weeks prior to the screening visit (Visit 1).
6. Vital signs to include temperature, pulse, respiratory rate and blood pressure. If a subject's baseline weight does not fluctuate by more than 10%, this weight can be used to calculate dose.
7. Adverse events and laboratory safety measurements will be graded per NCI CTCAE version 4.0. All adverse experiences, whether gradable by CTCAE or not, will also be evaluated for seriousness.
8. Routine laboratory tests (e.g., CBC with differential; comprehensive serum chemistry panel) will be performed by the local study site laboratory or their contract laboratory. CBC, serum chemistry and urinalysis may be collected up to 48 hours prior to any Cycle "X", Day 1 dosing.
9. PT/INR and aPTT should be collected at Screening and at the mandatory Safety Follow-up Visit after discontinuation of study therapy. Coagulation parameters should be determined throughout the study when clinically indicated. PT/INR and aPTT will be analyzed by the local study site laboratory.
10. For women of reproductive potential, a urine pregnancy test will be performed within 72 hours of the first dose. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required. Women who have been amenorrheaic for <2 years and who have not had a hysterectomy and oophorectomy will only be considered not to be of reproductive potential if they have a documented FSH value in the postmenopausal range.
11. FT3, FT4, TSH; at screening, every 4 cycles Q3W thereafter and at the mandatory Safety Follow-Up Visit. After screening, lab samples can be collected up to 48 hours prior to the scheduled time point.
12. Blood for anti-Pembrolizumab antibodies should be collected within 24 hours before start of study drug administration at Cycle 1, 2, 4, 6, and 8, and every 4 cycles thereafter before last dose of Pembrolizumab. Every effort should be made to collect additional blood samples for anti-Pembrolizumab antibodies at week 4 from the last dose of Pembrolizumab or until start of a new anti-cancer therapy, whichever occurs first. Analysis will be performed by a central laboratory.
13. PK samples will be collected pre-dose at Cycle 1, 2, 4, 6, and 8, and every 4 cycles thereafter. For single dose PK at Cycle 1 Day 1: pre-dose (-60 min to 0), post-dose (to +30 min), 6 (±30 min), 24, 48, 168, 336, and 504 (±2 hr for 24 to 504 hr) after completion of Pembrolizumab infusion. For PK at steady state after 22 weeks (Cycle 8), additional samples need to be collected on pre-dose (-60 min to 0), post-dose (to +30 min), 6 (±30 min), 24, 48, 168, 336, and 504 (±2 hr for 24 to 504 hr) after completion of Pembrolizumab infusion as appropriate to estimate $AUC_{0\text{-}21day}$ and C_{max} at steady state.
14. Testing will be performed by the local laboratory at Screening. Include HCV RNA (quantitative), HBsAg, and HIV 1/2 antibodies
15. Site must be able to provide documentation of the subject's tumor EGFR mutation and ALK translocation status if subject have ever done any of these tests.
16. The initial tumor imaging will be performed within 4 weeks prior to the date of randomization. Scans performed as part of routine clinical management are acceptable for use as the screening scan if they are of diagnostic quality and performed within 4 weeks prior to the first dose of trial treatment. Local reading (investigator assessment with site radiology reading) will be used to determine eligibility and for subject management. The Sponsor will collect radiological assessments for analysis by a central imaging vendor. The processes for image collection and transmission to the central vendor are in the Site Imaging Manual.
17. The first on-study imaging time point will be performed at 9 weeks (± 7 days) after the date of randomization, then every 9 weeks (± 7 days) thereafter, or more frequently if clinically indicated. Imaging timing should follow calendar days and should not be adjusted for delays in cycle starts. The same imaging technique should be used in a subject throughout the trial. On-study scans showing progression should be submitted immediately to the central imaging vendor and progressive disease should be verified by the central imaging vendor prior to subject discontinuation from treatment. Local reading (investigator assessment with site radiology reading) will be used to determine

eligibility and for subject management. The Sponsor will collect radiological assessments for analysis by a central imaging vendor. The processes for image collection and transmission to the central vendor are in the Site Imaging Manual.

18. In subjects who discontinue study therapy without centrally verified disease progression, a radiologic evaluation should be performed at the time of treatment discontinuation (i.e., date of discontinue ± 4 week window). If a previous scan was obtained within 4 weeks prior to the date of discontinuation, then a scan at treatment discontinuation isn't mandatory.
19. In subjects who discontinue study therapy without documented disease progression, every effort should be made to continue monitoring their disease status by radiologic imaging every 9 weeks (± 7 days) until (1) the start of new anti-cancer treatment, (2) disease progression, (3) death, or (4) the end of the study, whichever occurs first.
20. All doses will be administered via infusion on Day 1 of each cycle. Specific instructions for the administration procedures will be provided in the Procedures Manual.
21. Every effort should be made to collect blood samples for PK for up to 24 weeks after the last dose. In subjects who discontinue study therapy early without documented disease progression, every effort should be made to continue monitoring their disease status by radiologic imaging every 9 weeks (± 1 week) until the start of new anti-neoplastic therapy, disease progression, withdrawal of consent, death, or the end of the study, whichever occurs first; after the start of new anti-cancer treatment or documented disease progression by the central review, the subject should be contacted by telephone every 12 weeks (± 1 week) to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

6.2 Second Course Phase (Retreatment ONLY)

	Treatment Cycles								End of Treatment	Safety Follow-up[11]	Follow-up Visits[12]
Scheduling Window	Day 1 (±3); Every 21 Days									30 Days ± 3 Days after last dose	
Cycle (Week)	1 (0)	2 (3)	3 (6)	4 (9)	5 (12)	6 (15)	7 (18)	8 (21) and beyond			
Administrative Procedures											
Eligibility Criteria (See Section 7.1.5.2.1)	X										
Survival status											X
Clinical Procedures / Assessments											
Vital Signs/Weight[1]	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			
ECOG Performance Status	X	X	X	X	X	X	X	X	X	X	
Review Adverse Events[2]	X----------X										
Review Concomitant Medications	X----------X										
CBC with Differential[3]	X	X	X	X	X	X	X	X	X	X	
Comprehensive Serum Chemistry Panel[3]	X	X	X	X	X	X	X	X		X	
Coagulation Parameters[4]	X										
Urinalysis[5]	X									X	
Pregnancy Test - Urine or Serum HCG[6]	X										
Thyroid Function[7]	X				X						
Efficacy Measurements											
Tumor Imaging[8]	X			X			X		X[9]		X
Drug Administration											
Study Drug Administration[10]	X	X	X	X	X	X	X	X			

1. Vital signs to include temperature, pulse, respiratory rate and blood pressure. If a subject's baseline weight does not fluctuate by more than 10%, this weight can be used to calculate dose.
2. Adverse events and laboratory safety measurements will be graded per NCI CTCAE version 4.0. All adverse experiences, whether gradable by CTCAE or not, will also be evaluated for seriousness.
3. Routine laboratory tests (e.g., CBC with differential; comprehensive serum chemistry panel) will be performed by the local study site laboratory or their contract laboratory. CBC, serum chemistry and urinalysis may be collected up to 48 hours prior to any Cycle "X", Day 1 dosing.
4. PT/INR and aPTT should be collected prior to restarting treatment and at the mandatory Safety Follow-up Visit after discontinuation of study therapy. Coagulation parameters should be determined throughout the study when clinically indicated. PT/INR and aPTT will be analyzed by the local study site laboratory.
5. Routine laboratory tests (serum chemistry; hematology; urinalysis) should be performed within 10 days prior to restarting treatment. ECOG PS should be assessed within 3 days prior to the first dose of trial treatment.
6. For women of reproductive potential, a urine pregnancy test will be performed within 72 hours of the first retreatment dose. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required. Women who have been amenorrheaic for <2 years and who have not had a hysterectomy and oophorectomy will only be considered not to be of reproductive potential if they have a documented FSH value in the postmenopausal range.
7. FT3, FT4, TSH; prior to restarting treatment, every 4 cycles Q3W thereafter and at the mandatory Safety Follow-Up Visit. Lab samples can be collected up to 48 hours prior to the scheduled time point.
8. A scan must be performed within 21 days prior to restarting treatment with pembrolizumab. The first imaging time point in retreatment phase will be performed at 9 weeks (± 7 days) after the first dose, and then every 9 weeks (± 7 days) thereafter, or more frequently if clinically indicated. Imaging timing should follow calendar days and should not be adjusted for delays in cycle starts. The same imaging technique should be used in a subject throughout the trial. On-study scans showing progression should be submitted immediately to the central imaging vendor and progressive disease should be verified by the central imaging vendor prior to subject discontinuation from treatment. Local reading (investigator assessment with site radiology reading) will be used to determine eligibility and for subject management. The Sponsor will collect radiological assessments for analysis by a central imaging vendor. The processes for image collection and transmission to the central vendor are in the Site Imaging Manual.
9. In subjects who discontinue study therapy without centrally verified disease progression, a radiologic evaluation should be performed at the time of treatment discontinuation (i.e., date of discontinue ± 4 week window). If a previous scan was obtained within 4 weeks prior to the date of discontinuation, then a scan at treatment discontinuation isn't mandatory. In subjects who discontinue study therapy without documented disease progression, every effort should be made to continue monitoring their disease status by radiologic imaging every 9 weeks (± 7 days) until (1) the start of new anti-cancer treatment, (2) disease progression, (3) death, or (4) the end of the study, whichever occurs first.
10. All doses will be administered via infusion on Day 1 of each cycle. Specific instructions for the administration procedures will be provided in the Procedures Manual.
11. The mandatory Safety Follow-Up visit should be conducted 30 days (±3 days) after the last dose of study therapy (serious adverse events will be collected for up to 90 days after the end of treatment) or before the initiation of a new treatment, whichever comes first. Subjects who are discontinued from the study due to an unacceptable drug-related adverse event will be followed until the resolution of the adverse event (AE) to Grade 0-1 or stabilization or until beginning of a new therapy for their cancer, whichever occurs first.
12. In subjects who discontinue study therapy early without documented disease progression, every effort should be made to continue monitoring their disease status by radiologic imaging every 9 weeks (± 1 week) until the start of new anti-neoplastic therapy, disease progression, withdrawal of consent, death, or the end of the study, whichever occurs first; after the start of new anti-cancer treatment or documented disease progression by the central review, the subject should be contacted by telephone every 12 weeks (± 1 week) to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

7.0 TRIAL PROCEDURES

7.1 Trial Procedures

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

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

7.1.1 Administrative Procedures

7.1.1.1 Informed Consent

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

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.

7.1.1.2 Inclusion/Exclusion Criteria

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

7.1.1.3 Subject Identification Card

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

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

7.1.1.4 Medical History

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

7.1.1.4.1 Demographics

Demographics (including smoking history, tumor histological subtype, cancer-related gene mutation/translocation status, expression of cancer-related gene products, and cancer-related viral infection, etc.) will be obtained by the investigator or qualified designee.

Subject's tumor EGFR mutation and ALK translocation status will be obtained by the investigator or qualified designee, if subject have ever done any of these tests.

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 4 weeks before starting the trial therapy. In addition, record all treatments for a prior cancer other than the current cancer even if taken greater than 30 days prior to screening visit. Prior treatments for the current cancer will be recorded separately and not listed as a prior medication.

7.1.1.5.2 Concomitant Medications

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

7.1.1.6 Non-small cell lung cancer (NSCLC) Disease Details and Treatments

7.1.1.6.1 Disease Details

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

7.1.1.6.2 Prior Treatment

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

7.1.1.6.3 Subsequent Antineoplastic Therapy Status

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

7.1.1.7 Assignment of Screening Number

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

7.1.1.8 Assignment of Treatment/Randomization Number

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

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

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

The instructions for preparing and administering Pembrolizumab will be provided in the Procedures Manual.

7.1.2 Clinical Procedures/Assessments

7.1.2.1 Adverse Event Monitoring

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

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

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

7.1.2.2 Physical Exam

7.1.2.2.1 Full Physical Exam

The investigator or clinical designee will perform a full physical exam during the screening period. Clinically significant abnormal findings should be recorded as medical history. Additional full physical exams should be performed as specified in the 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/visits that do not require 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 dosing on Day 1 of each treatment cycle. New clinically significant abnormal findings should be recorded as AEs.

7.1.2.3 Height, Weight, and Vital Signs

The investigator or qualified designee will take weight and vital signs at screening, Cycle 1 Day 1 (predose), Day 8, Day 15, and Day 22, and predose of trial treatment in other subsequent cycles, discontinuation visit, and safety follow-up visit.

- Height (screening visit only)
- Weight
  - If a subject's weight at screening does not fluctuate by more than 10%, this weight can be used to calculate dose.
- Vital signs
  - Temperature
  - Pulse (in a sitting position)
  - Respiratory rate
  - Blood pressure (in a sitting position)
    - If blood pressure is >150/100 mmHg in a subject without a history of hypertension, or increased >20 mmHg (diastolic) from baseline measurement in a subject with a previous history of hypertension, the assessment should be repeated in 10 minutes for confirmation.

7.1.2.4 12-lead ECG

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

7.1.2.5 Eastern Cooperative Oncology Group (ECOG) Performance Status

The investigator or qualified designee will assess ECOG status (see Section 12.4) at screening, prior to the administration of trial treatment, discontinuation visit, and safety follow-up visit.

7.1.2.6 Tumor Imaging and Assessment of Disease

The process for image collection and transmission to the central vendor can be found in the Site Imaging Manual. Tumor imaging may be performed by computed tomography (CT) (preferred) or magnetic resonance imaging (MRI), but the same imaging technique should be used in a subject throughout the trial. CT scan is the more commonly used modality and is preferred for the majority of patients. An MRI can be utilized if clinically appropriate.

Imaging should include the chest, abdomen, and pelvis.

Local reading (investigator assessment with site radiology reading) based on RECIST 1.1 will be used to determine subject eligibility. The central imaging vendor will receive all images at the timepoints specified in the Study Flow Chart from the sites. All scans should be submitted to the central imaging vendor for evaluation and should be submitted in a timely fashion.

7.1.2.6.1 Initial Tumor Imaging

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

Scans performed as part of routine clinical management are acceptable for use as the screening scan if they are of diagnostic quality and performed within 28 days prior to the date of randomization.

7.1.2.6.2 Tumor Imaging During Trial

The first imaging assessment should be performed at 9 weeks (±7 days) from the date of randomization. Subsequent imaging should be performed every 9 weeks (±7 days) or more frequently if clinically indicated. Imaging should not be delayed for delays in cycle starts or extension of Pembrolizumab cycle intervals.

Per RECIST 1.1, partial or complete response should be confirmed by a repeat radiographic assessment not less than 4 weeks from the date the response was first documented. The scan for confirmation of response may be performed at the earliest 4 weeks after the first indication of response, or at the next scheduled scan, whichever is clinically indicated.

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

- Initial site-assessed disease progression is verified by the central imaging vendor
- The start of new anti-cancer treatment
- Withdrawal of consent
- Death
- The end of the study
  - Note: if the site-assessed disease progression is verified by the central vendors and the subject is clinically stable as per section 7.1.2.6.3.1, it is the discretion of the PI to continue to treat and image the subject at least 4 weeks after the first scan indicating progressive disease. irRECIST would then be followed by the site to determine if the follow-up scan confirms progressive disease (see Procedure Manual).

Subjects who have unconfirmed disease progression may continue on treatment and follow the regular imaging schedule intervals until progression is confirmed provided they have met the conditions detailed in Section 7.1.2.6.2.1.

7.1.2.6.2.1 irRECIST

As noted above, if site assessed PD has been verified by the central imaging vendor, the site may elect to continue treatment, repeat imaging ≥ 4 weeks later and assess tumor response or confirmed progression per irRECIST (see section 4.2.3.2 and Table 5).

Table 5 Imaging and Treatment after 1st radiologic evidence of PD

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

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

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

- irRECIST data will be collected in the clinical database.

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 to be drawn over the course of the trial (from pre-trial to post-trial visits), including approximate blood volumes drawn by visit and by sample type per subject can be found in Procedure Manual.

7.1.3.1 Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

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

Table 6 Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Blood	PT (INR)
Hemoglobin	Alkaline phosphatase	Glucose	aPTT
Platelet count	Alanine aminotransferase (ALT)	Protein	Free triiodothyronine (FT3)
WBC (total and differential)	Aspartate aminotransferase (AST)	Specific gravity	Free thyroxine (FT4)
Red blood cell count	Lactate dehydrogenase (LDH)	Microscopic exam, if abnormal results are noted	Thyroid stimulating hormone (TSH)
Absolute neutrophil Count	CRP		Serum/Urine β-human chorionic gonadotropin (β-hCG)
Absolute lymphocyte count	Creatinine or calculated creatinine clearance (CrCl)		FSH
	Uric acid		HIV antibody
	Calcium		HBsAg
	Chloride		HCV RNA
	Glucose		
	Phosphorus		
	Potassium		
	Sodium		
	Magnesium		
	Total bilirubin		
	Direct and indirect Bilirubin		
	Total protein		
	Blood urea nitrogen		
	Total cholesterol		
	Triglycerides		

Laboratory tests (hematology, serum chemistry, urinalysis, coagulation parameters, thyroid function) for screening or entry into the Second Course Phase should be performed within 10 days prior to the first dose of trial treatment. Laboratory tests (hematology, serum chemistry, urinalysis, and thyroid function) may be collected up to 48 hours prior to dosing in every cycle and the scheduled time points. The investigator or qualified designee must review the result and confirm acceptability of continuation of trial treatment.

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

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

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

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

7.1.3.2 Pharmacokinetic/Pharmacodynamic Evaluations

7.1.3.2.1 Blood Collection for Serum Pharmocokinetics of MK-3475

Serum samples for pharmacokinetics will be obtained at the following points (Table 7).

Table 7 Sampling Points for Pharmacokinetics

Sampling Point	Time window
Cycle 1 and Cycle 8	
Predose (Day 1)	Within 60 min prior to start of infusion
Postdose (Day 1)	Within 30 min after completion of infusion
6 hours after completion of infusion (Day 1)	±30 min
24 hours after completion of infusion (Day 2)	±2 hours
48 hours after completion of infusion (Day 3)	±2 hours
168 hours after completion of infusion (Day 8)	±2 hours
336 hours after completion of infusion (Day 15)	±2 hours
504 hours after completion of infusion (Day 22)	±2 hours
Cycle 2, 4, 6	
Predose on Day 1	Within 24 hours prior to start of infusion
After Cycle 8 and before last dose of Pembrolizumab (every 4 cycles)	
Predose on Day 1	Within 24 hours prior to start of infusion
Discontinuation	
Safety follow-up visit	
30 days after the last dose	±3 days
Follow-up visit	
6 months after the last dose	±7 days

Every effort should be made to collect additional blood samples for PK after the discontinuation visit for up to 6 months from the last dose of Pembrolizumab or until start of a new anti-cancer therapy, whichever occurs first. Serum sample preparation, storage and shipment instructions for plasma samples will be provided in the Procedure Manual.

7.1.3.2.2 Blood Collection for Serum Anti-Pembrolizumab Antibodies

Serum samples for serum anti-Pembrolizumab antibodies will be obtained at the following points (Table 8).

Table 8 Sampling Points for Anti-Pembrolizumab Antibodies

Sampling Point	Time window
Cycle 1, 2, 4, 6	
Predose on Day 1	Within 24 hours prior to start of infusion
Since Cycle 8 and before last dose of Pembrolizumab (every 4 cycles)	
Predose on Day 1	Within 24 hours prior to start of infusion
Discontinuation	
Safety follow-up visit	
30 days after the last dose	±3 days

Every effort should be made to collect additional blood samples for anti-Pembrolizumab antibodies at week 4 from the last dose of Pembrolizumab or until start of a new anti-cancer therapy, whichever occurs first. Serum sample preparation, storage and shipment instructions for plasma samples will be provided in the Procedure Manual.

7.1.4 Other Procedures

7.1.4.1 Withdrawal/Discontinuation

Subjects who discontinue/withdraw from treatment prior to completion of the treatment should be encouraged to continue to be followed for all remaining study visits.

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

7.1.4.2 Blinding/Unblinding

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

7.1.4.3 Calibration of Critical Equipment

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

Critical Equipment for this trial includes:

- Laboratory equipment – as required for inclusion labs and trial assessments
- Imaging equipment – as required for study objectives

- Safety equipment- as required for safety assessments
- Drug administration equipment- as required for storage, preparation and administration of study drugs

See protocol-specific Administrative Binder and Procedures Manual, Pharmacy Manual, operations/laboratory Manual and Site Imaging Manual.

7.1.5 Visit Requirements

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

7.1.5.1 Screening

UP to 28 days prior to first dose of trial treatment, 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 (hematology, serum chemistry, urinalysis, coagulation parameters, thyroid function test) for screening should be performed within 10 days prior to the first dose of trial treatment. ECOG PS should be assessed within 3 days prior to the first dose of trial treatment.
- Standard tumor markers (as appropriate for a given tumor type) will be collected within 14 days prior to the first dose of study treatment.
- For women of reproductive potential, a urine/serum 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 will be required.
- If results of HCV RNA (qualitative), HBsAg, and HIV 1/2 antibodies test obtained within 3 months before screening are available, data can be used in lieu of a screening procedure if performed within protocol specified timeframe and results meet criteria.

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

7.1.5.2 Treatment Period

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

7.1.5.2.1 Second Course Phase (Retreatment Period)

Subjects who stop pembrolizumab with SD or better may be eligible for up to 17 cycles (approximately 1 year) of additional pembrolizumab therapy if they progress after stopping pembrolizumab. This retreatment is termed the Second Course Phase of this study and is only available if the study remains open and the subject meets the following conditions:

- Either
    - Stopped initial treatment with pembrolizumab after attaining an investigator-determined confirmed CR according to RECIST 1.1.
        - Was treated for at least 8 cycles (approximately 24 weeks) with pembrolizumab before discontinuing therapy.
        - Received at least two treatments with pembrolizumab beyond the date when the initial CR was declared.

  OR

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

AND

- Experienced an investigator-determined confirmed radiographic disease progression after stopping their initial treatment with pembrolizumab.
- Did not receive any anti-cancer treatment since the last dose of pembrolizumab.
- Have a performance status of 0 or 1 on the ECOG Performance Scale.
- Demonstrate adequate organ function as detailed in Section 5.1.2.
- Female subject of childbearing potential should have a negative urine or serum pregnancy test within 72 hours prior to receiving retreatment with study medication.
- Female subjects of childbearing potential should be willing to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study medication (Reference Section 5.7.2). Subjects of child bearing potential are those who have not been surgically sterilized or have not been free from menses for > 1 year.
- Male subjects should agree to use an adequate method of contraception starting with the first dose of study therapy through 120 days after the last dose of study therapy.
- Does not have a history or current evidence of any condition, therapy, or laboratory abnormality that might interfere with the subject's participation for the full duration of the trial or is not in the best interest of the subject to participate, in the opinion of the treating investigator.

Subjects who restart treatment will be retreated at the same dose frequency as when they last received pembrolizumab. Treatment will be administered for up to 17 cycles (approximately 1 year). Visit requirements are outlined in Section 6.0 – Trial Flow Chart.

7.1.5.3 Discontinuation

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

7.1.5.4 Safety Follow-Up Visit

The mandatory safety follow-up visit will be conducted approximately 30 days after the last dose of trial treatment or before the initiation of a new antineoplastic treatment, whichever comes first. Subjects with an AE of Grade >1 will be further followed until the resolution of the AE to Grade 0-1 or until beginning of a new antineoplastic therapy, whichever occurs first.

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

7.1.5.5 Follow-Up Visit

Subjects who completed the safety follow-up visit will move to follow-up visit to collect serum samples for pharmacokinetics and anti-Pembrolizumab antibodies.

Subjects who discontinue trial treatment for a reason other than disease progression will be assessed every 9 weeks (± 1 week) by radiologic imaging to monitor disease status, until the start of new anti-cancer therapy, disease progression determined by the central review, death, or at end of study.

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

Once a subject experiences confirmed disease progression confirmed by central review or starts a new anti-cancer therapy, the subject should be contacted by telephone every 12 weeks (± 1 week) to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

7.1.5.6 Critical Procedures Based on Trial Objectives: Timing of Procedure

For this trial, the blood sample for MK-3475 is the critical procedure.

At any post-dose time-point, the blood sample for MK-3475 needs to be collected as close to the exact time-point as possible. All other procedures should be completed as close to the prescribed/scheduled time as possible. Trial procedures can be performed prior or after the prescribed/scheduled time.

The order of priority can be changed during the trial with joint agreement of the investigator and the Sponsor Clinical Director.

Any nonscheduled procedures required for urgent evaluation of safety concerns take precedence over all routine scheduled procedures.

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

For purposes of this trial, an overdose will be defined as any dose exceeding the prescribed dose for 1000 mg of pembrolizumab for patients allocated to the 2 mg/kg dose or 200 mg fixed dose, and > 20% of the calculated dose for patients allocated to the 10 mg/kg dose. No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, study treatment should be discontinued and the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

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

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

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

7.2.2 Reporting of Pregnancy and Lactation to the Sponsor

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

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

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

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

7.2.3 Immediate Reporting of Adverse Events to the Sponsor

7.2.3.1 Serious Adverse Events

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

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

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

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

Refer to Table 9 for additional details regarding each of the above criteria.

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

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

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

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

7.2.3.2 Events of Clinical Interest

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

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

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

Events of clinical interest for this trial include:

1. an overdose of Sponsor's product, as defined in Section 7.2.1 - Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor, that is not associated with clinical symptoms or abnormal laboratory results.
2. an elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

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

7.2.3.3 Protocol-Specific Exceptions to Serious Adverse Event Reporting

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

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

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

7.2.4 Evaluating Adverse Events

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

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

Table 9 Evaluating Adverse Events

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

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

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

7.2.5 Sponsor Responsibility for Reporting Adverse Events

All Adverse Events will be reported to regulatory authorities, IRB/IECs and investigators in accordance with all applicable global laws and regulations, i.e., per ICH Topic E6 (R1) Guidelines for Good Clinical Practice.

7.3 TRIAL GOVERNANCE AND OVERSIGHT

7.3.1 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.

8.0 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, but prior to any final database lock, 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, but prior to final database lock, will be documented in a supplemental SAP (sSAP) and referenced in the Clinical Study Report (CSR) for the study. Post-hoc exploratory analyses will be clearly identified in the CSR.

8.1 Statistical Analysis Plan Summary

8.1.1 Methods

8.1.1.1 Pharmacokinetics Analyses

Individual values will be listed for each PK parameter (e.g., $AUC_{0\text{-}28day}$, C_{max}, T_{max}, $t_{1/2}$ of single dose, C_{trough}, $AUC_{0\text{-}21day}$ and C_{max} at steady state of multiple dose) by treatment, and the following summary statistics will be provided: N (number of subjects with non-missing data), arithmetic mean, standard deviation, arithmetic percent CV (calculated as 100 x standard deviation/arithmetic mean), median, minimum, maximum, geometric mean, and geometric percent CV (calculated as 100 x sqrt($\exp(s^2) - 1$), where s^2 is the observed variance on the natural log-scale). Appropriate plots will be generated on pharmacokinetic profiles.

The Per-Protocol population (PP) will be used for the analysis of the PK data in this study，which will consist of all randomized subjects who received a Pembrolizumab dose and for whom at least one PK parameter can be calculated for the treatment period according to the protocol and who did not have any protocol deviation interfering with PK.

8.1.1.2 Efficacy Analyses

Anti-tumor activity will be evaluated as objective response rate (ORR), duration of response (DOR), progression-free survival (PFS), and overall survival (OS). ORR, DOR and PFS are evaluated per RECIST 1.1 and irRECIST by central radiologists' review.

For these anti-tumor activity endpoints, the All Subjects as Treated (ASaT) population will be used. The ASaT analysis population includes all randomized subjects that received at least one dose of study treatment. Subjects will be analyzed by treatment group according to actual treatment received. In addition, the ASaT analysis population for ORR includes subjects with measurable disease at baseline as assessed by central radiology review.

For each treatment arm, 95% confidence interval for ORR using exact binomial distribution will be provided.

8.1.1.3 Safety Analyses

The ASaT population will be used for the analysis of safety data in this study. The ASaT population consists of all subjects who received at least 1 dose of study treatment. Subjects will be analyzed by treatment group according to the treatment actual received. Adverse experiences will be summarized as counts and frequencies. Laboratory assessments, vital signs, and other safety endpoints will be summarized as appropriate.

8.1.2 Sample Size and Power Calculation

It is anticipated that approximately 42 subjects (14 subjects per dose/schedule) will be used to evaluate PK profiles. The rationale of selecting 14 subjects per dose level/schedule in the trial is to achieve at least 12 evaluable subjects in the Per-Protocol set to complete PK assessment adequately. Twelve subjects per dose level will ensure PK parameters can be reasonably estimated in this Chinese population. Randomization will be stratified by gender (male vs. female).

The between-subject standard deviation (log scale) was estimated based on the data from Pembrolizumab PN001. For 10mg/kg single dose (SD), between-subject standard deviation for $AUC_{0\text{-}28day}$ and C_{max} are 0.3029 ln (g•day/mL) and 0.3673 ln (g/mL) respectively. For 2mg/kg SD, the pooled between-subject standard deviation for $AUC_{0\text{-}28day}$ and C_{max} are 0.1938 ln (g•day/mL) and 0.2335 ln (g/mL) respectively. Standard deviation for multiple doses (MD) is similar as the one for SD. With 12 evaluable subjects, the half width of the 90% CI on the log scale for 10mg/kg $AUC_{0\text{-}21day}$ and C_{max} at steady state will be 0.157 and 0.190, for 2mg/kg $AUC_{0\text{-}21day}$ and C_{max} at steady state will be 0.101 and 0.121.

With 14 subjects on a dose/schedule, there is > 90% probability that at least two (2) subject with a G3-5 adverse event (AE) is observed if the underlying AE rate is 36%. In Pembrolizumab PN001 Part C, the observed G3-5 AE rate is approximately 36% for the Previously-Treated NSCLC Patients population.

With 14 subjects on a dose/schedule, there is > 95% probably that at least one (1) responder is observed, if the true response rate (RR) is 20%; there is > 90% probably that at least three (3) responders are observed, if the true response rate (RR) is 35%; there is > 90% probably that at least five (5) responders are observed, if the true response rate (RR) is 50%.

With 14 subjects, if the objective response rate is 50%, the 95% confidence interval (CI) is (0.23, 0.77). With 42 subjects overall, if the objective response rate is 50%, the 95% CI is (0.34, 0.66).

8.2 Statistical Analysis Plan

8.2.1 Responsibilities for Analyses

The statistical analysis of the data obtained from this study will be conducted by the Biostatistics and Research Decision Sciences (BARDS) statisticians located in MSD China, in collaboration with the Drug Metabolism and MSD China Clinical Research/Clinical Pharmacology Departments of the Sponsor.

8.2.2 Hypotheses/Estimation

Objectives are described in Sections 3.1 and 3.2.

8.2.3 Analysis Endpoints

8.2.3.1 Pharmacokinetic Endpoints

Single dose parameters: $AUC_{0\text{-}28days}$, C_{max}, T_{max}, and $t_{1/2,}$ etc.

Multiple dose parameters: C_{trough}, $AUC_{0\text{-}21day}$, and C_{max} at steady state.

8.2.3.2 Safety Endpoints

All clinical and laboratory safety measures of interests are described in Section 4.2.3.1.

8.2.3.3 Efficacy Endpoints

- Objective response rate (ORR) - RECIST 1.1 by central radiologists' review and irRECIST by central radiologists' review
    - ORR is defined as the proportion of subjects in the analysis population who have complete response (CR) or partial response (PR) using RECIST 1.1 criteria at any time during the study. Response for the analysis will be determined by central radiologists' review.
- Duration of Response (DOR) - RECIST 1.1 by central radiologists' review and irRECIST by central radiologists' review
    - For subjects who demonstrated CR or PR, response duration is defined as the time from first documented evidence of CR or PR until disease progression or death. Response duration for subjects who have not progressed or died at the time of analysis will be censored at the date of their last tumor assessment.
- Progression-free survival (PFS) - RECIST 1.1 by central radiologists' review and irRECIST by central radiologists' review
    - Progression-free-survival (PFS) is defined as the time from randomization to the first documented disease progression per RECIST 1.1 based on central radiologists' review or death due to any cause, whichever occurs first.

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

8.2.4 Analysis Populations

8.2.4.1 Efficacy Analysis Populations

The All Subjects as Treated (ASaT) population will be used for the analysis of ORR, DOR, PFS and OS. The ASaT analysis population includes all randomized subjects that received at least one dose of study treatment. Subjects will be analyzed by treatment group according to actual treatment received.

In addition, the ASaT analysis population for ORR includes subjects with measurable disease at baseline as assessed by central radiology review. The ASaT analysis population for DOR consists of all ORR ASaT analysis population responders.

Details on the approach to handling missing data are provided in Section 8.2.6 Statistical Methods.

8.2.4.2 Safety Analysis Populations

The All Subjects as Treated (ASaT) population will be used for the analysis of safety data in this study. The ASaT population consists of all randomized subjects who received at least one dose of study treatment. Subjects will be analyzed by treatment group according to the treatment actual received.

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

Details on the approach to handling missing data for safety analyses are provided in Section 8.2.6 Statistical Methods.

8.2.4.3 Pharmacokinetics Analysis Populations

The Per-Protocol population (PP) will be used for the analysis of the PK data in this study. The PP population will consist of all subjects who received a Pembrolizumab dose and for whom at least one pharmacokinetic parameter can be calculated for the treatment period according to the protocol and who did not have any protocol deviation interfering with PK.

8.2.5 Statistical Methods

8.2.5.1 Pharmacokinetics

Individual values will be listed for each PK parameter (e.g., $AUC_{0\text{-}28day}$, C_{max}, T_{max}, $t_{1/2}$ of single dose, C_{trough}, $AUC_{0\text{-}21day}$ and C_{max} at steady state of multiple dose) by treatment, and the following summary statistics will be provided: N (number of subjects with non-missing data), arithmetic mean, standard deviation, arithmetic percent CV (calculated as 100 x standard deviation/arithmetic mean), median, minimum, maximum, geometric mean, and geometric percent CV (calculated as 100 x sqrt($\exp(s^2)$ - 1), where s^2 is the observed

variance on the natural log-scale). Appropriate plots will be generated on pharmacokinetic profiles.

8.2.5.2 Statistical Methods for Safety Analyses

Safety and tolerability will be assessed by clinical review of all relevant parameters including adverse experiences (AEs), laboratory tests, and vital signs. Count and percentage of AE will be provided. Confidence interval for rate of AE of clinical interest will be estimated.

8.2.5.3 Statistical Methods for Efficacy Analyses

This section describes the statistical methods that address the objectives.

For the secondary efficacy endpoint of ORR based on central assessments using RECIST 1.1 and irRECIST, the point estimate, 95% confidence interval will be provided using exact binomial method proposed by Clopper and Pearson (1934) [11]. Subjects in the primary analysis population (ASaT) without response data will be counted as non-responder.

For DOR, PFS and OS endpoints, Kaplan-Meier (KM) curves and median estimates from the KM curves will be provided as appropriate. Table 10 summarizes the efficacy analyses methods.

Table 10 Analysis Strategy for Efficacy Variables

Endpoint/Variable‡ (Description, Time Point)	Statistical Method	Analysis Population	Missing Data Approach
Secondary Endpoints			
ORR (central radiologists' review, RECIST 1.1 and irRECIST)	Exact method based on binomial distribution	ASaT	Subjects with missing data are considered non-responders
DOR (central radiologists' review, RECIST 1.1 and irRECIST)	Summary statistics using Kaplan-Meier method	All responders	Non-responders are excluded in analysis
PFS (central radiologists' review, RECIST 1.1 and irRECIST)	Summary statistics using Kaplan-Meier method	ASaT	Censored at last assessment
Overall survival (OS)	Summary statistics using Kaplan-Meier method	ASaT	Censored at last know alive date

8.2.6 Multiplicity

No multiplicity adjustment procedures will be used to control for statistical Type I error (i.e. false positive rate).

8.2.7 Sample Size and Power Calculations

It is anticipated that approximately 42 subjects (14 subjects per dose/schedule) will be used to evaluate the PK profiles. The rationale of selecting 14 subjects per dose level/schedule in the trial is to achieve at least 12 evaluable subjects in the Per-Protocol set to complete PK

assessment adequately. Twelve subjects per dose level will ensure the PK parameters reasonably estimated in Chinese.

The between-subject standard deviation (log scale) was estimated based on the data from Pembrolizumab PN001. For 10mg/kg single dose (SD), between-subject standard deviation for $AUC_{0\text{-}28day}$ and C_{max} are 0.3029 ln (g•day/mL) and 0.3673 ln (g/mL) respectively. For 2mg/kg SD, The pooled between-subject standard deviation for $AUC_{0\text{-}28day}$ and C_{max} are 0.1938 ln (g•day/mL) and 0.2335 ln(g/mL) respectively. Standard deviation for multiple doses (MD) is similar as the one for SD. With 12 evaluable subjects, the half width of the 90% CI on the log scale for 10mg/kg $AUC_{0\text{-}21day}$ and C_{max} at steady state will be 0.157 and 0.190, for 2mg/kg $AUC_{0\text{-}21day}$ and C_{max} at steady state will be 0.101 and 0.121.

With 14 subjects on a dose/schedule, there is > 90% probability that at least two (2) subject with a G3-5 adverse event (AE) is observed if the underlying AE rate is 36%. In Pembrolizumab PN001 Part C, the observed G3-5 AE rate is approximately 36% for the Previously-Treated NSCLC Patients population.

With 14 subjects on a dose/schedule, there is > 95% probability that at least one (1) responder is observed, if the true response rate (RR) is 20%; there is > 90% probability that at least three (3) responders are observed, if the true response rate (RR) is 35%; there is > 90% probability that at least five (5) responders are observed, if the true response rate (RR) is 50%.

With 14 subjects, if the objective response rate is 50%, the 95% confidence interval (CI) is (0.23, 0.77). With 42 subjects overall, if the objective response rate is 50%, the 95% CI is (0.34, 0.66).

8.2.8 Summaries of Baseline Characteristics, Demographics, and Other Analyses

The number and percentage of subjects screened, enrolled, the primary reasons for screening failure, and the primary reason for discontinuation will be displayed. Demographic variables, baseline characteristics, primary and secondary diagnoses, and prior and concomitant therapies will be summarized by treatment either by descriptive statistics or categorical tables in all enrolled subjects.

8.2.9 Subgroup Analyses and Effect of Baseline Factors

The estimate of the treatment effect for the secondary endpoints will be estimated and plotted within each category of the following classification variables:

- Age category (≤65 vs. >65 years)
- Gender (Male vs. Female)
- ECOG Performance Scale (0 vs. 1)
- Disease Status (Locally advanced vs. Metastatic)
- Histological subtype (squamous vs. non-squamous)
- ALK translocation status (translocated vs. wild type)
- EGFR mutation status (mutant vs. wild type)

The consistency of the treatment effect will be assessed descriptively via summary statistics by category for the classification variables listed above.

8.2.10 Interim Analyses

No interim analysis is planned in this trial.

Primary pharmacokinetics analysis will be performed after Cycle 1 to obtain single dose pharmacokinetics profile.

The final analysis for multiple dose pharmacokinetics and efficacy will be performed after Cycle 8 when all randomized patients have either blood samples collected in Cycle 8 or discontinued from study, whichever occurs earlier.

8.2.11 Compliance (Medication Adherence)

Drug accountability data for Pembrolizumab will be collected during the study. Any deviation fromprotocol-directed administration will be reported.

8.2.12 Extent of Exposure

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

9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.1 Investigational Product

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

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

Table 11 Product Descriptions

Product Name & Potency	Dosage Form
Pembrolizumab 100 mg / 4 mL	Solution for Infusion

9.2 Packaging and Labeling Information

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

Pembrolizumab (MK-3475) will be provided as a kitted supply.

9.3 Clinical Supplies Disclosure

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

9.4 Storage and Handling Requirements

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

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

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

9.5 Discard/Destruction/Returns and Reconciliation

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

9.6 Standard Policies

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

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

10.1 Confidentiality

10.1.1 Confidentiality of Data

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

10.1.2 Confidentiality of Subject Records

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

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

10.1.3 Confidentiality of Investigator Information

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

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

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

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

10.1.4 Confidentiality of IRB/IEC Information

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

10.2 Compliance with Financial Disclosure Requirements

Financial Disclosure requirements are outlined in the US Food and Drug Administration Regulations, Financial Disclosure by Clinical Investigators (21 CFR Part 54). It is the

Sponsor's responsibility to determine, based on these regulations, whether a request for Financial Disclosure information is required. It is the investigator's/subinvestigator's responsibility to comply with any such request.

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

10.3 Compliance with Law, Audit and Debarment

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

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

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

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

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

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

The investigator must maintain copies of all documentation and records relating to the conduct of the trial in compliance with all applicable legal and regulatory requirements. This

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

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

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

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

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

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

10.4 Compliance with Trial Registration and Results Posting Requirements

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

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

10.5 Quality Management System

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

10.6 Data Management

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

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

10.7 Publications

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

primary outcome, 12 months after the decision to discontinue development, or product marketing (dispensed, administered, delivered or promoted), whichever is later.

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

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

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

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

11.0 LIST OF REFERENCES

1. Greenwald RJ, Freeman GJ, Sharpe AH. The B7 family revisited. Annu Rev Immunol 2005; 23:515-48.
2. Okazaki T, Maeda A, Nishimura H, Kurosaki T, Honjo T. PD-1 immunoreceptor inhibits B cell receptor-mediated signaling by recruiting src homology 2-domaincontaining tyrosine phosphatase 2 to phosphotyrosine. Proc Natl Acad Sci USA 2001; 98:13866-71.
3. Thompson RH, Dong H, Lohse CM, Leibovich BC, Blute ML, Cheville JC, et al. PD-1 is expressed by tumor-infiltrating immune cells and is associated with poor outcome for patients with renal cell carcinoma. Clin Cancer Res 2007; 13:1757-61.
4. Gao Q, Wang XY, Qiu SJ, Yamato I, Sho M, Nakajima Y, et al. Overexpression of PD-L1 significantly associates with tumor aggressiveness and postoperative recurrence in human hepatocellular carcinoma. Clin Cancer Res 2009; 15:971-9.
5. Hamanishi J, Mandai M, Iwasaki M, Okazaki T, Tanaka Y, Yamaguchi K, et al. Programmed cell death 1 ligand 1 and tumor-infiltrating CD8+ T lymphocytes are prognostic factors of human ovarian cancer. Proc Natl Acad Sci USA 2007; 104:3360-5.
6. Mu CY, Huang JA, Chen Y, Chen C, Zhang XG. High expression of PD-L1 in lung cancer may contribute to poor prognosis and tumor cells immune escape through suppressing tumor infiltrating dendritic cells maturation. Med Oncol. 2011; 28:682-8.
7. Zhang Y, Huang S, Gong D, Qin Y and Shen Q. Programmed death-1 upregulation is correlated with dysfunction of tumor-infiltrating CD8+ T lymphocytes in human non-small cell lung cancer. Cell Mol Immunol. 2010; 7:389–395.
8. Noboru Yamamoto, Hiroshi Nokihara, Yasuhide Yamada, Hajime Asahina, takeshi Shibata, Yosuke Tamura et al. Biomarker & developmental therapeutics. The 10th annual meeting Japanese society of medical oncology 2012 July 26-28;Osaka, Japan
9. Sulpher JA, Owen SP, Hon H, et al. Factors influencing a specific histologic diagnosis of non-small cell lung cancer. ASCO annual meeting 2011 June 3-7;Illinois, USA
10. Nadjafi M, Santos GDC, Le L, Hwang D, Tsao MS, Leighl NB. Diagnostic patterns of nsclc at Princess Margaret Hospital. J Clin Oncol 2011;29:(suppl; abstr e18027)
11. Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of bnomial. Biometrika 1934; 26: 404-13.

12.0 APPENDICES

12.1 Merck Code of Conduct for Clinical Trials

Merck*
Code of Conduct for Clinical Trials

I. Introduction

A. Purpose

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

B. Scope

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

II. Scientific Issues

A. Trial Conduct

1. Trial Design

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

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

2. Site Selection

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

3. Site Monitoring/Scientific Integrity

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

B. Publication and Authorship

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

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

III. Subject Protection

A. IRB/ERC review

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

B. Safety

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

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

C. Confidentiality

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

D. Genomic Research

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

IV. Financial Considerations

A. Payments to Investigators

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

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

B. Clinical Research Funding

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

C. Funding for Travel and Other Requests

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

V. Investigator Commitment

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

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

12.2 ECOG Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.
5	Dead.
* As published in Am. J. Clin. Oncol.: Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982. The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.	

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

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

REFERENCE

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

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

13.0 SIGNATURES

13.1 Sponsor's Representative

TYPED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	

13.2 Investigator

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

TYPED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	