| | |
|---|---|
| **Official Protocol Title:** | A Phase 3, Randomized, Double-Blind Study of Pembrolizumab plus Ipilimumab vs Pembrolizumab plus Placebo in Previously Untreated, Stage IV, Metastatic Non-small Cell Lung Cancer Subjects Whose Tumors are PD-L1 Positive (TPS ≥ 50%) (KEYNOTE-598) |
| **NCT number:** | NCT03302234 |
| **Document Date:** | 11-Dec-2020 |

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

**TITLE:**

A Phase 3, Randomized, Double-Blind Study of Pembrolizumab plus Ipilimumab vs Pembrolizumab plus Placebo in Previously Untreated, Stage IV, Metastatic Non-small Cell Lung Cancer Subjects Whose Tumors are PD-L1 Positive (TPS ≥ 50%) (KEYNOTE-598)

**IND NUMBER:** 132864
**EudraCT NUMBER:** 2016-004364-20

**NCT NUMBER:** NCT03302234

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## DOCUMENT HISTORY

| Document | Date of Issue | Overall Rationale |
|---|---|---|
| MK-3475-598-06 | 11-DEC-2020 | Data from IA1 of KEYNOTE-598 (data cutoff: 01-SEP-2020) indicated that the study did not meet the prespecified success criteria for improvement in PFS or OS for the combination of pembrolizumab plus ipilimumab compared with pembrolizumab plus placebo. Furthermore, a nonbinding futility analysis was performed at IA1 at the request of the eDMC. This analysis showed the study met the criteria for declaring futility and the benefit-risk assessment was not considered positive to continue the trial. Based upon these data and at the recommendation of the eDMC, MSD implemented this amendment to direct all ipilimumab and placebo administrations to stop, and to unblind the study. The study will remain open so ongoing subjects will have continued access to pembrolizumab. |
| MK-3475-598-05 | 14-JUL-2020 | To update the assumptions and the timing of interim analyses (IA) in the Statistical Analysis Plan (SAP), and to include a Patient-reported Outcomes (PRO) secondary objective, endpoint, and statistical method for analysis. |
| MK-3475-598-04 | 14-FEB-2020 | The primary reasons for this amendment is to update assumptions in the SAP. |
| MK-3475-598-03 | 15-FEB-2018 | The primary reasons for this amendment were to add a new exploratory objective (Objective 8) to evaluate the immunogenicity, exposure, antidrug antibodies (ADA), and pharmacokinetic (PK) samples; to add a new Exclusion Criterion #25 "Has known ROS1 mutation: if treatment and testing for ROS1 is approved and accessible."; and to add required thyroid (TSH, FT3/T3, FT4/T4) and adrenal (ACTH) function monitoring before to each dose of ipilimumab/placebo. Other clarifications and minor revisions were also included. |

| Document | Date of Issue | Overall Rationale |
|---|---|---|
| MK-3475-598-02 | 4-DEC-2017 | The primary reason for this amendment was to update the background information and rational for the dose and regiment of ipilimumab based on input from regulatory agencies. Additional revisions and clarifications were made to align with the pembrolizumab program template and updated risk language. |
| MK-3475-598-01 | 10-OCT-2017 | The primary reasons for this amendment was to implement revisions recommended by regulatory agencies, including updates to the rationales for the selected population, dose regimen for ipilimumab, and the use of a comparator. Agency requests also included adding the specific IHC assay to Inclusion Criterion #8, clarifying Exclusion #24, updating test describing urine pregnancy testing, adding pembrolizumab dose medication guidance for myocarditis, adding a 550 mL cap to the amount of blood drawn over an 8-week period, and clarified that PD-L1 testing would be performed by a central laboratory. Additional updates and clarifications included the removal of the PFS2 exploratory endpoint and associated monitoring, and changes to align with the pembrolizumab program template. |
| MK-3475-598-00 | 28-JUL-2017 | Original protocol. |

## SUMMARY OF CHANGES

**PRIMARY REASON(S) FOR THIS AMENDMENT:**

**Amendment: 06**

**Overall Rationale for the Amendment:** Data from IA1 of KEYNOTE-598 (data cutoff: 01-SEP-2020) indicated that the study did not meet the prespecified success criteria for improvement in PFS or OS for the combination of pembrolizumab plus ipilimumab compared with pembrolizumab plus placebo. Furthermore, a nonbinding futility analysis was performed at IA1 at the request of the eDMC. This analysis showed the study met the criteria for declaring futility and the benefit-risk assessment was not considered positive to continue the trial. Based upon these data and at the recommendation of the eDMC, MSD implemented this amendment to direct all ipilimumab and placebo administrations to stop and to unblind the study. The study will remain open so ongoing subjects will have continued access to pembrolizumab.

| Section Numbers | Section Titles | Description of Changes | Rationale |
|---|---|---|---|
| 1 | Trial Summary | Revised text, tables, and figures to remove ipilimumab and placebo references, as well as assessments/procedures specific to these treatments. Added clarifying notes to subsections. | In accordance with the overall rationale for the Amendment, ipilimumab and matching placebo have been removed from the study. |
| 2 | Trial Design | | |
| 5.2 | Trial Treatments | | |
| 5.8 | Subject Withdrawal/Discontinuation Criteria | | |
| 7.1.3.1 | Laboratory Safety Evaluations | | |
| 9 | Labeling, Packaging, Storage and Return of Clinical Supplies | | |

| Section Numbers | Section Titles | Description of Changes | Rationale |
|---|---|---|---|
| 4.2.2.1.2 | Rationale for Dose and Regimen of Ipilimumab/Placebo in Combination With Pembrolizumab | Added note to clarify that no further subjects will be randomized in the study and these sections are no longer applicable. | Ipilimumab and matching placebo have been removed from the study. |
| 5.3 | Randomization or Treatment Allocation | | |
| 4.2.3.2 | Patient-reported Outcomes | Added note to clarify that PROs will no longer be collected. | In accordance with the overall rationale for the amendment, PROs, pharmacokinetic, pharmacodynamic, and immunogenicity are no longer required. |
| 7.1.2.8 | Patient-reported Outcomes | Deleted section content and added a note to clarify. | |
| 7.1.3.3 | Pharmacokinetic/ Pharmacodynamic/ Immunogenicity Evaluations | | |
| 4.3 | Benefit/Risk | Added note to clarify that the benefit-risk assessment of ipilimumab is no longer applicable and related text has been removed. | In accordance with the overall rationale for the amendment, the benefit/risk assessment of ipilimumab is no longer applicable. |
| 5.2.3 | Trial Blinding | Added note to clarify that blinding and emergency unblinding are no longer applicable. All subjects will receive open-label pembrolizumab monotherapy. | Ipilimumab and matching placebo have been removed from the study and the study has been unblinded. |
| 7.1.4.2 | Subject Blinding/Unblinding | | |

| Section Numbers | Section Titles | Description of Changes | Rationale |
|---|---|---|---|
| 5.10 | Beginning and End of the Trial | Added language to state that upon study completion, subjects are discontinued and may be enrolled in a pembrolizumab extension study, if available. | Subjects may be enrolled in a pembrolizumab extension study upon study completion. |
| 6 | Trial Flow Chart | Revised tables to remove assessments/procedures specific to ipilimumab and placebo treatments. Added a clarifying note. | In accordance with the overall rationale for the amendment, all references to ipilimumab and placebo, as well as assessments/procedures specific to these treatments, are removed from the protocol. |
| 7.1.5.6 | Second Course Phase | Revised text to remove ipilimumab and placebo references, as well as assessments/procedures specific to these treatments. Added a clarifying note. | Ipilimumab and matching placebo have been removed from the study. |
| 7.2.1 | Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor | | |
| 8 | Statistical Analysis Plan | Added notes to clarify that a nonbinding futility analysis planned for IA2 was performed at IA1 at the request of the eDMC, the study has been unblinded, and no further prespecified analysis of primary and secondary endpoints will be performed. | In accordance with the overall rationale for the amendment. |

| Section Numbers | Section Titles | Description of Changes | Rationale |
|---|---|---|---|
| 7.2.7 | Data Monitoring Committee | Added a statement that no additional eDMC reviews will take place. | In accordance with the overall rationale for the amendment. |
| 8.7.1 | Interim Safety Analyses | | |
| 8.8.4 | Safety Analyses | | |
| 5.1.2 | Subject Inclusion Criteria | Added note to clarify that contraception is no longer required for male participants and sperm donation is acceptable. | Since ipilimumab have been removed from the study, male contraception is no longer required. |
| 12.5 | Contraceptive Guidance and Pregnancy Testing | | |
| Throughout | Throughout | All references to ipilimumab and placebo were removed. Where deletion of text could cause confusion due to the original design of the study, the text has been left unchanged and a note was added. | In accordance with the overall rationale for the amendment. |
| | | Made typographical corrections and minor administrative edits. | To correct typographical errors and clarify intended meaning. |

No additional changes.

## 1.0 TRIAL SUMMARY

| | |
|---|---|
| Abbreviated Title | Phase 3 1L Study of Pembrolizumab ± Ipilimumab in NSCLC |
| Sponsor Product Identifiers | MK-3475<br>Pembrolizumab |
| Trial Phase | 3 |
| Clinical Indication | First-line treatment of Stage IV metastatic programmed cell death-ligand 1 (PD-L1) positive (TPS ≥50%) NSCLC |
| Trial Type | Interventional |
| Type of control | Active control with placebo<br>**NOTE: As of Amendment 06, active control with placebo has been removed.** |
| Route of administration | Intravenous (IV) |
| Trial Blinding | Double-blind<br>**NOTE: As of Amendment 06, the study is unblinded.** |
| Treatment Groups | Pembrolizumab (MK-3475) 200 mg IV every 3 weeks (Q3W) + ipilimumab 1 mg/kg IV every 6 weeks (Q6W)<br>**OR**<br>Pembrolizumab (MK-3475) Q3W 200 mg IV + Placebo IV Q6W<br>**NOTE: As of Amendment 06, ipilimumab and matching placebo have been removed from the treatment groups. Subjects remaining on treatment will receive open-label pembrolizumab monotherapy as per protocol.** |
| Number of trial subjects | Approximately 568 subjects will be enrolled. |
| Estimated duration of trial | The Sponsor estimates that the trial will require approximately 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 | **NOTE: As of Amendment 06, this section has been updated.**<br>Each subject will participate in the trial for approximately 3 years from the time the subject signs the informed consent form through the final contact.<br>After a screening phase of 30 days, each subject will be assigned to receive trial treatment until disease progression is radiographically documented and verified by blinded independent central review (BICR), when clinically appropriate, confirmed by the site per modified Response Evaluation Criteria in Solid Tumors 1.1 for immune-based therapeutics (iRECIST), unacceptable AEs, intercurrent illness that prevents further administration of treatment, investigator's decision to discontinue the subject, noncompliance with trial treatment or procedures requirements, administrative reasons requiring cessation of treatment, withdrawal of consent, or until the subject has received 35 administrations of pembrolizumab (approximately 2 years). Subjects who stop trial treatment after receiving 35 administrations of pembrolizumab for reasons other than disease progression or intolerability, or subjects who attain a complete response and stop trial treatment may be eligible for up to 17 additional administrations of pembrolizumab (approximately 1 year) upon experiencing disease progression, (Section 7.1.5.6 – Second Course Phase). |

| | |
|---|---|
| | After the end of treatment, each subject will be followed for the occurrence of AEs and spontaneously reported pregnancy as described under Section 7.2 – Assessing and Recording Adverse Events of the protocol.<br>At the end of treatment, each subject will be followed for a minimum of 30 days for AE monitoring. Serious AEs occurring within 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, will be collected, whichever is earlier. Subjects will have post-treatment follow-up for disease status, including initiating a nonstudy cancer treatment and experiencing disease progression, until death, withdrawing consent, or becoming lost to follow-up.<br>Subjects who discontinue for reasons other than disease progression will have post-treatment follow-up for disease status until disease progression radiographically per RECIST 1.1, verified by BICR, initiating a nonstudy cancer treatment, withdrawing consent, or becoming lost to follow-up. All subjects will be followed by telephone for OS until death, withdrawal of consent, or the end of the study. |
| Randomization Ratio | 1:1 |

A list of abbreviations used in this document can be found in Section 12.6 – List of Abbreviations.

## 2.0 TRIAL DESIGN

### 2.1 Trial Design

**NOTE: As of Amendment 06, ipilimumab and matching placebo have been removed from the study. Subjects who remain on treatment will receive open-label pembrolizumab monotherapy as per protocol. This section has been amended and assessments no longer required have been deleted.**

The original study design was a Phase 3, randomized, double-blind study to evaluate the efficacy of pembrolizumab plus ipilimumab vs pembrolizumab plus placebo for first-line (1L) treatment of subjects with Stage IV, metastatic NSCLC whose tumors are programmed death-ligand 1 (PD-L1) positive (Tumor Proportion Score [TPS] ≥50%) and lack *epidermal growth factor receptor* (*EGFR*)-sensitizing mutations and *anaplastic lymphoma kinase* (*ALK*) translocations.

Approximately 568 subjects with previously untreated, Stage IV metastatic NSCLC whose tumors are PD-L1 positive (TPS ≥50%) and in whom *EGFR*- or *ALK*-directed therapy is not indicated were projected to be enrolled in this trial for examination of the efficacy and safety of pembrolizumab plus ipilimumab versus pembrolizumab plus placebo. Subjects were randomized in a 1:1 ratio to receive pembrolizumab plus ipilimumab or pembrolizumab plus placebo.

The subjects were stratified prior to randomization by ECOG Performance Status (0 versus 1), geographic region of the enrolling site (East Asia versus non-East Asia), and predominant tumor histology (squamous versus nonsquamous) (see Section 5.4 – Stratification for more details).

**As of Amendment 06,** ipilimumab and matching placebo have been removed from the study. All subjects remaining on treatment in the study will receive open-label pembrolizumab monotherapy.

Subjects will be evaluated with radiographic imaging to assess response to treatment every 9 weeks (63 ± 7 days) from randomization through 54 weeks, then every 12 weeks (84 days ±7 days) subsequently. All imaging obtained on study will be submitted to the imaging vendor for BICR, which will assess the images using RECIST 1.1 (see Section 7.1.2.6.5) for determination of ORR, PFS, and DOR. Initial tumor imaging showing site-assessed progressive disease (PD) should be submitted immediately for verification by BICR prior to treatment discontinuation. Treatment-based decisions may utilize modified RECIST 1.1 for immune-based therapeutics (iRECIST), as described in the Merck Imaging Tip Sheet and in Section 7.1.2.6.6. AE monitoring will be ongoing throughout the trial and graded in severity according to the guidelines outlined in the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. Treatment with pembrolizumab will continue until 35 trial treatments of pembrolizumab have been administered, documented disease progression, unacceptable AEs, intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw the subject, intolerable toxicity, subject withdraws consent, pregnancy of the subject, noncompliance with trial treatment or procedure requirements, or administrative reasons.

Subjects treated with pembrolizumab who attain a confirmed complete response (CR), or who complete 35 administrations of pembrolizumab without demonstrating disease progression or intolerability to treatment, may be eligible for retreatment with pembrolizumab only after they have experienced radiographic disease progression according to defined criteria in Section 7.1.5.6; this retreatment will be the Second Course Phase. Response or progression in the Second Course Phase will not count towards the ORR and PFS endpoints in this trial.

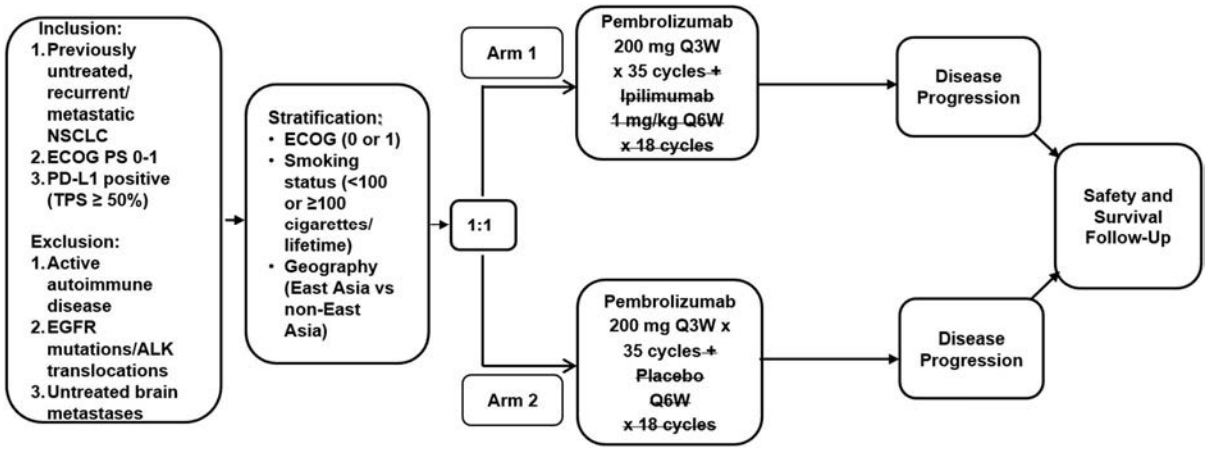
Subjects will have post-treatment follow-up for disease status, including initiating a nonstudy cancer treatment and experiencing disease progression, until death, withdrawing consent, or becoming lost to follow-up.

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 original study design randomized subjects into 2 treatment arms: pembrolizumab plus ipilimumab and pembrolizumab plus matching placebo (Figure 1). The design of the Second Course of treatment is depicted in Figure 2. **As of Amendment 06, ipilimumab and matching placebo have been removed from the study, as depicted in Figure 1and Figure 2.**

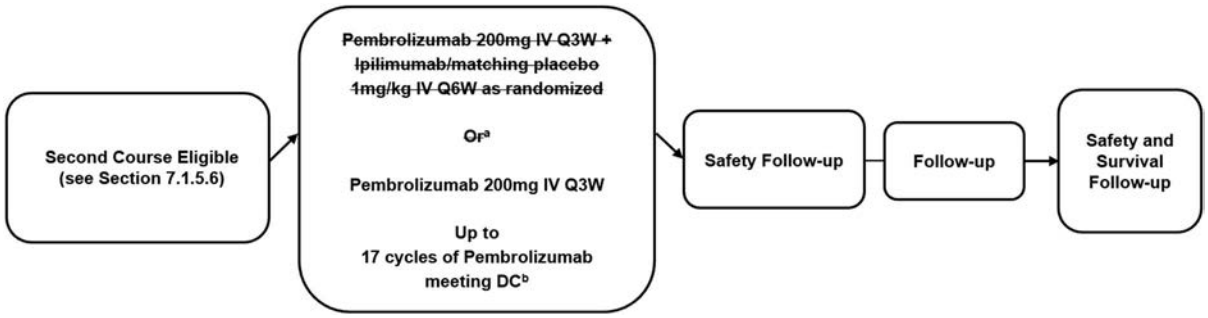
Figure 1 Trial Design Overview




**Note:** As of Amendment 06, ipilimumab and matching placebo were removed from the study, as indicated by strikethrough.

Abbreviations: ALK=anaplastic lymphoma kinase; ECOG=Eastern Cooperative Oncology Group; EGFR=epidermal growth factor receptor; NSCLC=nonsmall cell lung cancer; PD-L1=Programmed death-ligand 1; PS=Performance scale; Q3W=every 3 weeks; Q6W=every 6 weeks.

Figure 2 Second Course Overview




**Note**: As of Amendment 06, ipilimumab and matching placebo were removed from the study, as indicated by strikethrough.

Abbreviations: DC=discontinuation; IV=intravenous; Q3W=every 3 weeks; Q6W=every 6 weeks.
a At the discretion of the principal investigator. Original treatment arm will remain blinded.
b Discontinuation criteria are listed in Section 5.8.

## 3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

In previously untreated subjects with Stage IV, metastatic PD-L1 positive (TPS ≥50%) NSCLC:

### 3.1 Primary Objective(s) & Hypothesis(es)

1. **Objective**: To compare the OS in subjects treated with pembrolizumab plus ipilimumab versus pembrolizumab plus placebo

   **Hypothesis**: Pembrolizumab plus ipilimumab demonstrates superior OS compared to pembrolizumab plus placebo

2. **Objective**: To compare the PFS per RECIST 1.1 based on BICR in subjects treated with pembrolizumab plus ipilimumab versus pembrolizumab plus placebo

   **Hypothesis**: Pembrolizumab plus ipilimumab demonstrates superior PFS per RECIST 1.1 (based on BICR) compared to pembrolizumab plus placebo

The study is considered to have met its primary objective if pembrolizumab plus ipilimumab is superior to pembrolizumab plus placebo in PFS or OS at an IA or FA.

### 3.2 Secondary Objective(s) & Hypothesis(es)

1. **Objective**: To compare the confirmed ORR per RECIST 1.1 based on BICR in subjects treated with pembrolizumab plus ipilimumab versus pembrolizumab plus placebo

   **Hypothesis**: Pembrolizumab plus ipilimumab demonstrates superior confirmed ORR per RECIST 1.1 (based on BICR) compared to pembrolizumab plus placebo

2. **Objective**: To evaluate the DOR per RECIST 1.1 (based on BICR) in subjects treated with pembrolizumab plus ipilimumab and pembrolizumab plus placebo.

3. **Objective**: To evaluate the mean change from baseline in EORTC QLQ-C30 global health status/quality of life score (items 29 and 30) in subjects treated with pembrolizumab plus ipilimumab compared to pembrolizumab plus placebo.

4. **Objective**: To evaluate TTD in the composite endpoint of cough (European Organization for Research and Treatment of Cancer Quality of Life Questionnaire and Lung Cancer Module 13 [EORTC QLQ-LC13] Q1), pain in chest (EORTC QLQ LC13 Q10), and shortness of breath (EORTC QLQ-C30 Q8) in subjects treated with pembrolizumab plus ipilimumab and pembrolizumab plus placebo.

5. **Objective**: To evaluate the safety and tolerability profile of pembrolizumab plus ipilimumab in subjects treated with pembrolizumab plus ipilimumab.

### 3.3 Exploratory Objectives

1. **Objective**: To evaluate patient-reported outcomes using the EORTC QLQ-C30, EORTC QLQ-LC13, and the EQ-VAS in subjects treated with pembrolizumab plus ipilimumab compared to pembrolizumab plus placebo.

2. **Objective**: To evaluate clinically meaningful thresholds for change in cough, pain in chest, and shortness of breath from the EORTC QLQ-LC13/QLQ-QC30 questionnaires using Patient Global Impression of Change – Lung Symptoms Questionnaire (PGIC-L).

3. **Objective**: To evaluate clinically meaningful thresholds for change in lung cancer symptoms from the NSCLC-SAQ Questionnaire using the Patient Global Impression of Severity – Lung Cancer Symptoms (PGIS-LC) Questionnaire and the Patient Global Impression of Change – Lung Cancer Symptoms (PGIC-LC) questionnaires.

4. **Objective**: To characterize utilities using the EQ-5D-5L.

5. **Objective**: To conduct psychometric analyses on the NSCLC Symptom Assessment Questionnaire (SAQ).

6. **Objective**: To evaluate PFS and ORR using modified RECIST 1.1 for immune-based therapeutics (iRECIST) [1], as assessed by the investigator in subjects treated with pembrolizumab plus ipilimumab compared to pembrolizumab plus placebo.

7. **Objective:** To identify molecular (genomic, metabolic, and/or proteomic) biomarkers that may be indicative of clinical response/resistance, safety, pharmacodynamic activity, and/or the mechanism of action of pembrolizumab and other treatments.

8. **Objective:** To evaluate the immunogenicity and exposure of pembrolizumab and ipilimumab and the drug-drug effects of pembrolizumab and ipilimumab used in combination by analysis of ADA and pharmacokinetic (PK) samples.

## 4.0 BACKGROUND & RATIONALE

### 4.1 Background

Pembrolizumab is a potent humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) with high specificity of binding to the programmed cell death 1 (PD-1) receptor, thus inhibiting its interaction with PD-L1 and programmed cell death ligand 2 (PD-L2). Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an IV immunotherapy for advanced malignancies. Keytruda® (pembrolizumab) is indicated for the treatment of patients across a number of indications. For more details on specific indications, refer to the IB.

Refer to the IB/approved labeling for detailed background information on MK-3475.

### 4.1.1 Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades [2]. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes in cancer tissue and favorable prognosis in various malignancies [2]. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells/FoxP3+ regulatory T-cells seems to correlate with improved prognosis and long-term survival in solid malignancies such as ovarian, colorectal, and pancreatic cancer; hepatocellular carcinoma; malignant melanoma; and renal cell carcinoma (RCC). Tumor-infiltrating lymphocytes can be expanded ex vivo and reinfused, inducing durable objective tumor responses in cancers such as melanoma [3] [4].

The programmed cell death protein-1 (PD-1) receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. Programmed cell death protein-1 (encoded by the gene Pdcd1) is an Ig superfamily member related to CD28 and CTLA-4 that has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or programmed death-ligand 2 [PD-L2]) [5] [6].

The mechanism by which PD-1 down modulates T-cell responses is similar to, but distinct from that of CTLA-4, as both molecules regulate an overlapping set of signaling proteins [7] [8]. Programmed cell death protein-1 was shown to be expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B-cells, T regs, and natural killer cells [9] [10]. The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types, including non-hematopoietic tissues as well as in various tumors [8] [11] [12] [13]. Both ligands are type I transmembrane receptors containing both IgV- and IgC-like domains in the extracellular region and contain short cytoplasmic regions with no known signaling motifs. Binding of either PD-1 ligand to PD-1 inhibits T-cell activation triggered through the T-cell receptor. Programmed death-ligand 1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments. Programmed death-ligand 2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T-cell function in peripheral tissues [11]. Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. High expression of PD-L1 on tumor cells (and to a lesser extent of PD-L2) has been found to correlate with poor prognosis and survival in various cancer types, including RCC [14], pancreatic carcinoma [15], hepatocellular carcinoma [16], and ovarian carcinoma [4]. Furthermore, PD-1 has been suggested to regulate tumor-specific T-cell expansion in subjects with melanoma [3].

Antimouse PD-1 or antimouse PD-L1 antibodies have demonstrated antitumor responses as a monotherapy in models of squamous cell carcinoma, pancreatic carcinoma, melanoma, and colorectal carcinoma. Blockade of the PD-1 pathway effectively promoted CD8+ T-cell infiltration into the tumor and the presence of interferon-gamma, granzyme B and perforin, indicating that the mechanism of action involved local infiltration and activation of effector T-cell function in vivo [15] [17] [18] [19] [20] [21].

In-house experiments have confirmed the in vivo efficacy of PD-1 blockade as a monotherapy as well as in combination with chemotherapy in syngeneic mouse tumor models (see the IB).

### 4.1.2 Summary of Pembrolizumab Clinical Activities

#### 4.1.2.1 Completed Clinical Trials

Four clinical studies have been conducted to evaluate the efficacy of pembrolizumab monotherapy in the treatment of NSCLC: KEYNOTE-001, KEYNOTE-010, KEYNOTE-024, and KEYNOTE-042.

**KEYNOTE-001**:

An open-label Phase 1 trial (KEYNOTE-001) was conducted to evaluate the safety and clinical activity of single-agent pembrolizumab. The dose escalation portion of this trial evaluated 3 dose levels, 1 mg/kg, 3 mg/kg, and 10 mg/kg, administered every 2 weeks (Q2W), in subjects with advanced solid tumors. All 3 dose levels were well tolerated and no dose-limiting toxicities were observed. Based on 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). All cohorts have completed enrollment.

In KEYNOTE-001, a total of 550 NSCLC subjects were treated in several dose expansion cohorts with at least 1 dose of pembrolizumab. The initial data from 495 NSCLC subjects were published and reported. The ORR was 19.4% (18.0% in the 394 previously treated subjects and 24.8% in the 101 previously untreated subjects). The response rate (RR) was similar regardless of dose, schedule, and histologic analysis. Current or former smokers had a RR of 22.5%, as compared with 10.3% among subjects who had never smoked cigarettes.

Subjects were required to submit a newly obtained tumor biopsy prior to initiating therapy with pembrolizumab to evaluate the tumors for expression of PD-L1. After evaluation of several methods for pathological assessment, in a training set, membranous PD-L1 expression in at least 50% of tumor cells (TPS ≥50%) was selected as the cutoff point defining PD-L1 high. In a validation set of 313 subjects, the RR was 45.2% in the 73 subjects with a TPS ≥50%, including 43.9% in previously treated subjects and 50% in previously untreated subjects, values that numerically exceeded the RR in the training group [22].

Pembrolizumab has been generally well tolerated. The most common treatment-related AEs were fatigue (19.4%), pruritus (10.7%), and decreased appetite (10.5%). AEs of Grade 3 or higher were reported in 47 of 495 patients (9.5%). The only treatment-related AEs of an inflammatory or immune-mediated nature that occurred in more than 2% of patients were infusion-related reactions (in 15 patients [3.0%]), hypothyroidism (in 34 patients [6.9%]), and pneumonitis (in 18 patients [3.6%]). One infusion reaction led to treatment discontinuation. All the patients with hypothyroidism were successfully treated with medical therapy [22].

**KEYNOTE-010**:

KEYNOTE-010 was a randomized, adaptively designed Phase 2/3 trial of pembrolizumab at 2 dose levels versus docetaxel in subjects with NSCLC with PD-L1 positive tumors who had experienced disease progression after platinum-containing systemic therapy. Subjects were randomized according to their TPS (extent of PD-L1 expression) defined as follows: a TPS ≥50% was considered strongly positive and a TPS = 1% to 49% was considered weakly positive. Approximately 920 subjects were planned to be enrolled in this trial to examine the efficacy compared of pembrolizumab to docetaxel in an enriched population.

Overall, the results from KEYNOTE-001 and KEYNOTE-010 demonstrated that pembrolizumab provided substantial, clinically meaningful benefits in OS, PFS, and ORR in subjects with NSCLC who progressed after platinum-containing chemotherapy and whose tumor cells expressed PD-L1. The PD-L1 selection employed in KEYNOTE-010 identified patients more likely to benefit from pembrolizumab and resulted in favorable hazard ratios (HR) in OS compared to docetaxel.

In previously treated subjects with NSCLC with PD-L1, TPS ≥1%, and disease progression following platinum-containing chemotherapy, pembrolizumab provides a statistically significant and clinically meaningful OS benefit compared to standard docetaxel chemotherapy.

In KEYNOTE-010, pembrolizumab was superior to docetaxel in the strongly positive TPS ≥ 50% stratum with regard to OS, with an HR of 0.54 (p = 0.00024) and 0.50 (p = 0.00002) for pembrolizumab 2 mg/kg Q3W versus docetaxel and 10 mg/kg Q3W versus docetaxel, respectively [23]. Pembrolizumab was superior to docetaxel in the overall positive TPS ≥ 1% population with regard to OS, with an HR of 0.71 (p = 0.00076) and 0.61 ($p$<0.00001) for pembrolizumab 2 mg/kg Q3W and 10 mg/kg Q3W, respectively. Pembrolizumab was superior to docetaxel in the strongly positive TPS ≥ 50% stratum with regard to PFS by independent review committee based on RECIST 1.1, with an HR of 0.58 (p = 0.00009) and 0.59 (p = 0.00007) for pembrolizumab 2 mg/kg Q3W and 10 mg/kg Q3W, respectively, compared to docetaxel. Pembrolizumab provided numerically superior benefit in PFS by independent review committee based on RECIST 1.1 compared to docetaxel in the overall positive TPS ≥1% population, with an HR of 0.88 and 0.79 for pembrolizumab 2 mg/kg Q3W and 10 mg/kg Q3W, respectively; however, the differences were not statistically significant at the 0.001 level required per protocol.

**KEYNOTE-024**:

KEYNOTE-024 was a multicenter, international, randomized, open-label, controlled trial of intravenous (IV) pembrolizumab monotherapy versus the choice of multiple standard of care (SOC) platinum-based chemotherapies in subjects previously untreated for their Stage IV NSCLC and whose tumors expressed PD-L1 at ≥50%. First-line treatment with pembrolizumab significantly prolonged PFS (HR 0.50; 95% confidence interval [CI]: 0.37, 0.68; $p$<0.001) and OS (HR 0.60; 95% CI: 0.41, 0.89; p = 0.005) compared with SOC chemotherapy, inclusive of pemetrexed maintenance for subjects with nonsquamous tumors [24]. In addition, pembrolizumab was associated with a higher ORR, including a higher CR rate, as well as a longer DOR as compared to SOC. Pembrolizumab was better tolerated than chemotherapy and AEs were easily managed. The observed safety profile of the

pembrolizumab arm was consistent with the safety profile for pembrolizumab established to date. Based on the mechanism of action of pembrolizumab, immune-mediated AEs, including pneumonitis occurred at a greater frequency with pembrolizumab compared to chemotherapy. Most immune-mediated events were of Grade 1 or 2 severity, and none led to death. These data underscore the substantial benefit of pembrolizumab as initial therapy for subjects with previously untreated, advanced NSCLC whose tumors express high levels of PD-L1 (TPS ≥50%).

**KEYNOTE-042**:

KEYNOTE-042, a randomized, open-label, Phase 3 study, compared pembrolizumab monotherapy to SOC platinum-based chemotherapy in previously untreated participants with advanced or metastatic NSCLC whose tumors express PD-L1 TPS ≥1%. This study confirmed the OS treatment effect of pembrolizumab monotherapy observed in participants with TPS ≥50% NSCLC in KEYNOTE-024, and extended these benefits to a broader population with TPS ≥1% NSCLC. Results from the FA of KEYNOTE-042 indicated a significant OS benefit for pembrolizumab over platinum-doublet therapy, with a HR of 0.82 (95% CI, 0.71-0.93) for PD-L1 TPS ≥1%, and HR of 0.70 (95% CI, 0.58-0.86) for PD-L1 TPS ≥50%. Median OS was 16.4 months (95% CI, 14.0-19.7 months) with pembrolizumab and 12.1 months (95% CI, 11.3-13.3 months) with platinum-doublet in PD-L1 TPS ≥1%. In the population with PD-L1 TPS ≥50%, median OS was 20.0 months (95% CI, 15.9-24.2 months) with pembrolizumab and 12.2 months (95% CI, 10.4-14.6 months) with platinum-doublet. There was no observed PFS benefit with pembrolizumab versus chemotherapy, with PFS HR of 0.83 (95% CI, 0.69-1.00), and median PFS of 6.5 months (95% CI, 5.9-8.5 months) with pembrolizumab and 6.4 months (95% CI, 6.2-7.2 months) with platinum-doublet in PD-L1 TPS ≥50% [25]. The ORR was 39.1% vs 32% pembrolizumab vs chemotherapy in PD-L1 TPS ≥50% population [26].

#### 4.1.2.2 Ongoing Clinical Trials with Pembrolizumab

Several additional studies to evaluate the efficacy of pembrolizumab combination therapy in the treatment of NSCLC are in progress. Refer to the current pembrolizumab IB for a description of ongoing studies.

## 4.2 Rationale

### 4.2.1 Rationale for the Trial and Selected Subject Population

The global incidence for lung cancer was 1.8 million in 2012, resulting in an estimated 1.6 million deaths [27]. NSCLC accounts for approximately 85% of all lung cancer cases. Progress has been made in the clinical management of early stage NSCLC by establishing comprehensive, multimodality treatment regimens; however, the prognosis for advanced disease has not improved substantially. With an overall 5-year survival rate of 9% to 13%, the treatment of NSCLC remains a highly unmet medical need. Cytotoxic chemotherapy as single agents or in combination has served as the mainstay of treatment for decades with platinum-containing doublets and maintenance strategies conferring the greatest advances in OS gains.

KEYNOTE-024 established pembrolizumab as first-line therapy for patients with metastatic NSCLC whose tumors express high PD-L1 (TPS ≥50%) and with no *EGFR* or *ALK* genomic tumor aberrations. While the benefit observed in the trial was substantial with significant improvement in PFS and OS, the benefits may be improved in this patient population.

In CheckMate 026, a total of 541 patients were randomized to treatment. In patients with ≥ 5% PD-L1 expression (n = 423), nivolumab did not improve PFS over platinum-doublet chemotherapy (HR, 1.15; 95% confidence interval [CI] 0.91 to 1.45; p = 0.25) [28]. Median PFS was 4.2 months and 5.9 months with nivolumab and investigator's choice (IC) of platinum-based doublet chemotherapy, respectively. Among all treated patients, any CTCAE Grade AEs and Grade 3 or 4 treatment-related AEs were 71% and 18% with nivolumab, as compared to 92% and 51% with IC platinum-based doublet chemotherapy, respectively. Nivolumab did not show superior PFS when compared to IC platinum-based doublet chemotherapy as first-line therapy in Stage IV/recurrent NSCLC patients with ≥5% PD-L1 tumor expression. The safety profile of nivolumab was favorable to IC platinum-based doublet chemotherapy and consistent with that reported in previous studies.

While monotherapy pembrolizumab provides efficacy in patients with metastatic NSCLC whose tumors express high PD-L1 (TPS ≥50%), there is still medical need to further improve on the efficacy observed with PD-1 monotherapy in a biomarker selected population, reduce the time to response, and improve symptom control. Therefore, the combination of another therapy with pembrolizumab should be explored. The blocking of PD-1 receptors and CTLA4 receptors results in T-lymphocytes being fully disinhibited. Preclinical studies have demonstrated synergy between nivolumab and ipilimumab. A clinical trial in patients with advanced NSCLC has shown antitumor activity when combining these 2 checkpoint inhibitors in CheckMate 012. Patients who had not received prior chemotherapy or immunotherapy with recurrent Stage IIIB or IV NSCLC were randomly assigned to nivolumab 1 mg/kg every 2 weeks (Q2W) plus ipilimumab 1 mg/kg every 6 weeks (Q6W), nivolumab 3 mg/kg Q2W plus ipilimumab 1 mg/kg every 12 weeks (Q12W), or nivolumab 3 mg/kg Q2W plus ipilimumab 1 mg/kg Q6W. Seventy-eight patients were randomized into the last 2 arms and the data from these patients are summarized here. One patient assigned to ipilimumab Q6W did not begin treatment because of rapid clinical deterioration. The median follow-up times were 12.8 months (IQR 9.3, 15.5) and 11.8 months (IQR 6.7, 15.9) for the ipilimumab Q12W and Q6W arms, respectively. Table 1 shows the ORRs by investigator per RECIST 1.1 for the 2 nivolumab and ipilimumab cohorts. Of the 6 patients with 50% or more tumor cells staining for PD-L1 in their baseline tumor sample who were treated with ipilimumab 1 mg/kg Q12W, all (100%) had an objective response. Of the 7 patients with 50% or more tumor cells staining for PD-L1 in their baseline tumor sample who were treated with ipilimumab 1 mg/kg Q6W, 6 (83%) patients had an objective response [29].

As presented at American Society of Clinical Oncologists (ASCO) 2017, with longer follow up of 2 years, and using pooled data from arms of ipilimumab Q12W and Q6W in combination with nivolumab (77 total number of patients, 47 patients with PD-L1 ≥1%, 13 patients with PD-L1 ≥50%), ORR was 43% (compared to 23% in nivolumab monotherapy) in all treated patients, and 57% and 92% in patients with ≥1% and ≥50% tumor PD-L1 expression, respectively. Both OS and PFS showed clinical benefits in all patients, those with ≥1%, and in those with ≥50% tumor PDL1 expression. The OS rates at 2

years were 49%, 58%, and 62%, respectively, in each group. The PFS rates at 2 years were 29%, 38%, and 54% in each group, respectively. With the limitation of a very small number of patients whose tumors express PD-L1 ≥50% (13 patients); these data suggest that the PD-L1 status of the tumor may predict those patients most likely to benefit from the combination treatment [30].

Table 1 Objective Response Rate and Duration of Response for Patients Who Received Nivolumab 3 mg/kg Q2W and Ipilimumab 1 mg/kg by Investigator Review per RECIST 1.1

| | **Nivolumab Plus Ipilimumab Q12W** | **Nivolumab Plus Ipilimumab Q6W** |
|---|---|---|
| | **All Patients (N=38)** | **All Patients (N=39)** |
| ORR, n (%) [95% CI] | 18 (47) [31, 64] | 15 (38) [23, 55] |
| DCR, n (%) [95% CI] | 30 (79) [63, 90] | 22 (56) [40, 72] |
| Best overall response, n (%) | | |
| CR | 0 (0) | 0 (0) |
| PR | 18 (47) | 15 (38) |
| SD | 12 (32) | 7 (18) |
| PD | 5 (13) | 11 (28) |
| Unable to Determine | 3 (8) | 6 (15) |
| DOR median (range), months | NR (11.3, NR) | NR (8.4, NR) |

Abbreviations: CR=complete response; DCR=disease control rate; NR=not reached; ORR=objective response rate; PD=progressive disease; PR=partial response; Q2W=every 2 weeks, RECIST=Response Evaluation Criteria in Solid Tumors; SD=stable disease.

The combination regimen was tolerable in this patient population. Treatment-related AEs were reported as Grade 1-2 in 17 (45%), Grade 3 in 13 (34%), and Grade 4 in 1 (3%) of the 38 patients who received nivolumab 3 mg/kg plus ipilimumab 1 mg/kg Q12W and as Grade 1 to 2 in 15 (38%), Grade 3 in 11 (28%), and Grade 4 in 2 (5%) of the patients who received nivolumab 3 mg/kg Q2W plus ipilimumab 1 mg/kg Q6W. The most frequent treatment-related Grade 3 to 4 AEs were increased lipase 3 (8%) on the nivolumab 3 mg/kg Q2W plus ipilimumab 1 mg/kg Q12W arm and adrenal insufficiency 2 (5%) and colitis 2 (5%) on the nivolumab 3 mg/kg Q2W plus ipilimumab 1 mg/kg Q6W arm. Nine patients (24%) discontinued treatment because of AEs in the nivolumab 3 mg/kg Q2W plus ipilimumab Q12W arm and 7 patients (18%) discontinued treatment because of AEs in the nivolumab 3 mg/kg Q2W plus ipilimumab Q6W arm. There were no treatment-related deaths. Table 2 summarizes select potentially immune-mediated AEs, which were consistent with monotherapy nivolumab or ipilimumab. The toxicity was manageable.

Also with longer follow up as presented in ASCO 2017, and using pooled nivolumab plus ipilimumab Q12W/Q6W, any CTCAE Grade TRAE was reported in 79% compared to 73% in the nivolumab only cohort, TRAE Grade 3-4 was 36% compared to 19% in the nivolumab only cohort. Treatment-related AEs leading to discontinuation was reported in 18% of pooled

nivolumab plus ipilimumab Q12W/Q6W, when compared to 12% in the nivolumab monotherapy cohort.

Table 2 Potential Immune-Mediated Adverse Events Among Patients Treated With Nivolumab 3 mg/kg Q2W Plus Ipilimumab 1 mg/kg

| | **Nivolumab Plus Ipilimumab Q12W, All Patients (N=38) n (%)** | | | **Nivolumab Plus Ipilimumab Q6W, All Patients (N=39) n (%)** | | |
|---|---|---|---|---|---|---|
| | **Grade 1-2** | **Grade 3** | **Grade 4** | **Grade 1-2** | **Grade 3** | **Grade 4** |
| **Endocrine** | **3 (8)** | **1 (3)** | **0 (0)** | **6 (15)** | **2 (5)** | **0 (0)** |
| Adrenal Insufficiency | 0 (0) | 1 (3) | 0 (0) | 3 (8) | 2 (5) | 0 (0) |
| Hyperthyroidism | 0 (0) | 0 (0) | 0 (0) | 4 (10) | 0 (0) | 0 (0) |
| **Gastrointestinal** | **7 (18)** | **2 (5)** | **0 (0)** | **7 (18)** | **2 (5)** | **0 (0)** |
| Diarrhea | 7 (18) | 1 (3) | 0 (0) | 8 (21) | 0 (0) | 0 (0) |
| Colitis | 0 (0) | 1 (3) | 0 (0) | 1 (3) | 2 (5) | 0 (0) |
| **Hepatic** | **1 (3)** | **0 (0)** | **0 (0)** | **0 (0)** | **1 (3)** | **1 (3)** |
| Increased Alanine Aminotransferase | 1 (3) | 0 (0) | 0 (0) | 0 (0) | 1(3) | 0 (0) |
| Increased Aspartate Aminotransferase | 1 (3) | 0 (0) | 0 (0) | 0 (0) | 1 (3) | 0 (0) |
| Increased transaminases | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 1 (3) |
| **Pneumonitis** | **2 (5)** | **2 (5)** | **0 (0)** | **1 (3)** | **1 (3)** | **0 (0)** |
| **Renal** | **1 (3)** | **2 (5)** | **0 (0)** | **3 (8)** | **0 (0)** | **0 (0)** |
| Acute Kidney Injury | 1 (3) | 1 (3) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| Increased blood creatinine | 1 (3) | 1 (3) | 0 (0) | 3 (8) | 0 (0) | 0 (0) |
| **Skin** | **14 (37)** | **1 (3)** | **0 (0)** | **12 (31)** | **2 (5)** | **0 (0)** |
| Pruritus | 9 (24) | 0 (0) | 0 (0) | 5 (13) | 0 (0) | 0 (0) |
| Maculopapular Rash | 5 (13) | 0 (0) | 0 (0) | 3 (8) | 1 (3) | 0 (0) |
| Rash | 5 (13) | 1 (3) | 0 (0) | 3 (8) | 1 (3) | 0 (0) |
| Generalized Rash | 0 (0) | 0 (0) | 0 (0) | 4 (10) | 0 (0) | 0 (0) |

Considering the entire efficacy and safety data, the combination of an anti-PD-1 mAb and an anti-CTLA4 mAb is a reasonable regimen to evaluate in a first-line treatment setting compared to the established SOC of pembrolizumab monotherapy for subjects whose PD-L1 TPS ≥50%. Details regarding specific benefits and risks for subjects participating in this clinical trial may be found in the accompanying IB and informed consent documents.

### 4.2.2 Rationale for Dose Selection/Regimen/Modification

#### 4.2.2.1 Justification for Treatment Regimen

##### 4.2.2.1.1 Rationale for Fixed Dose Pembrolizumab

The planned dose of pembrolizumab for this study is 200 mg every 3 weeks (Q3W). Based on the totality of data generated in the Keytruda development program, 200 mg Q3W is the appropriate dose of pembrolizumab for adults across all indications and regardless of tumor type. As outlined below, this dose is justified by:

- Clinical data from 8 randomized studies demonstrating flat dose- and exposure-efficacy relationships from 2 mg/kg Q3W to 10 mg/kg every 2 weeks (Q2W),
- Clinical data showing meaningful improvement in benefit-risk including OS at 200 mg Q3W across multiple indications, and
- Pharmacology data showing full target saturation in both systemic circulation (inferred from pharmacokinetic [PK] data) and tumor (inferred from physiologically-based pharmacokinetic [PBPK] analysis) at 200 mg Q3W.

Among the 8 randomized dose-comparison studies, a total of 2262 participants were enrolled with melanoma and NSCLC, covering different disease settings (treatment-naïve, previously treated, PD-L1 enriched, and all-comers) and different treatment settings (monotherapy and in combination with chemotherapy). Five studies compared 2 mg/kg Q3W versus 10 mg/kg Q3W (KN001 Cohort B2, KN001 Cohort D, KN002, KN010, and KN021), and 3 studies compared 10 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B3, KN001 Cohort F2 and KN006). All of these studies demonstrated flat dose- and exposure-response relationships across the doses studied representing an approximate 5- to 7.5-fold difference in exposure. The 2 mg/kg (or 200 mg fixed dose) Q3W provided similar responses to the highest doses studied. Subsequently, flat dose-exposure-response relationships were also observed in other tumor types including head and neck cancer, bladder cancer, gastric cancer and classical Hodgkin Lymphoma, confirming 200 mg Q3W as the appropriate dose independent of the tumor type. These findings are consistent with the mechanism of action of pembrolizumab, which acts by interaction with immune cells, and not via direct binding to cancer cells.

Additionally, pharmacology data clearly show target saturation at 200 mg Q3W. First, PK data in KN001 evaluating target-mediated drug disposition (TMDD) conclusively demonstrated saturation of PD-1 in systemic circulation at doses much lower than 200 mg Q3W. Second, a PBPK analysis was conducted to predict tumor PD-1 saturation over a wide range of tumor penetration and PD-1 expression. This evaluation concluded that pembrolizumab at 200 mg Q3W achieves full PD-1 saturation in both blood and tumor.

Finally, population PK analysis of pembrolizumab, which characterized the influence of body weight and other participant covariates on exposure, has shown that the fixed-dosing provides similar control of PK variability as weight based dosing, with considerable overlap in the distribution of exposures from the 200 mg Q3W fixed dose and 2 mg/kg Q3W dose. Supported by these PK characteristics, and given that fixed-dose has advantages of reduced

dosing complexity and reduced potential of dosing errors, the 200 mg Q3W fixed-dose was selected for evaluation across all pembrolizumab protocols.

#### 4.2.2.1.2 Rationale for Dose and Regimen of Ipilimumab/Placebo in Combination With Pembrolizumab

**NOTE: As of Amendment 06, ipilimumab and matching placebo have been removed from the study. This section is no longer applicable.**

Ipilimumab is currently approved for melanoma patients alone, and in combination with the anti-PD1 antibody. Ipilimumab has demonstrated efficacy with doses ranging from 1 mg/kg to 10 mg/kg, with lower toxicity rates at lower doses. In addition, in adjuvant melanoma IV ipilimumab is approved at 10 mg/kg every 12 weeks for up to 3 years or until documented disease recurrence or unacceptable toxicity.

The ipilimumab dose selected for the current study KEYNOTE-598, 1 mg /kg, was formed on the basis of having a well-tolerated safety profile in combination with pembrolizumab, improved ORR (30%), and durable DCR (55%) observed in KEYNOTE 021 Cohorts D and H. Cohort D focused on establishing a safe dose for the combination, while Cohort H was designed to generate preliminary efficacy data of the combination. Key eligibility criteria for Cohorts D and H included age ≥18 years; advanced or metastatic NSCLC of any histology; ≥1 prior therapy (including ≥1 line of platinum-doublet chemotherapy); ECOG Performance Status 0 or 1; ≥1 measurable lesion; any PD-L1 status; any *EGFR* or *ALK* status; no prior anti-PD-1, anti-PD-L1, or anti–CTLA-4 therapy; no autoimmune disease; and no current interstitial lung disease or prior interstitial lung disease requiring steroids. Patients with *EGFR*-sensitizing mutation or *ALK* translocation were required to have had prior treatment with the appropriate targeted therapy. Initially, a 3+3 dose escalation design was pursued for adding 4 treatments of ipilimumab to a constant dose of pembrolizumab every 3 weeks for a total of 2 years in Cohort D. Three subjects were treated at pembrolizumab 10 mg/kg Q3W and ipilimumab 1 mg/kg Q3W and then 3 additional subjects were treated at pembrolizumab 10 mg/kg Q3W and ipilimumab 3 mg/kg Q3W. Although no dose-limiting toxicities were observed, the dose of the combination was changed to pembrolizumab 2 mg/kg Q3W and ipilimumab 1 mg/kg Q3W x 4 doses because of emerging concerns regarding the safety, including some treatment-related deaths, of subjects with NSCLC treated with labeled doses of ipilimumab in combination with nivolumab. Forty-five subjects were treated at this lower dose of both agents.

Forty-four subjects were available for the efficacy assessment because one was later identified as having melanoma instead of NSCLC. The median duration of follow-up was 11.3 months (0.3-26.9 months). The ORR was 30%, one of which was CR (2%), by independent central review per RECIST 1.1, as shown in Table 3.

Table 3 Objective Response Rate and Duration of Response for Subjects Who Received Pembrolizumab 2 mg/kg Q3W and Ipilimumab 1 mg/kg by Independent, Central Review per RECIST 1.1

| | **Pembrolizumab 2 mg/kg + Ipilimumab 1 mg/kg (n=44)** | | | |
|---|---|---|---|---|
| | **Total Population n=44** | **TPS ≥50% n=6** | **TPS ≥1% n=24** | **TPS <1% n=20** |
| ORR, n (%) [95% CI] | 13 (30) [17-45] | 1 (17) [<1-64] | 8 (33) [16-55] | 5 (25) [9-49] |
| DCR, n (%) [95% CI] | 24 (55) [39-70] | 2 (33) [4-78] | 13 (54) [33-74] | 11 (55) [32-77] |
| Best overall response, n (%) | | | | |
| CR | 1 (2) | 0 | 0 | 1 (5) |
| PR | 12 (27) | 1(17) | 8 (33) | 4 (20) |
| SD | 11 (25) | 1 (17) | 5 (21) | 6 (30) |
| PD | 13 (30) | 2(33) | 6 (25) | 7 (35) |
| Not evaluable | 7 (16) | 2 (33) | 5 (21) | 2 (10) |
| DOR median (range), months | 10.5 (2.5+ to 21.0) | 3.5 (3.5 to 3.5) | 15.3 (3.5 to 21) | 7.7 (2.5+ to 10.7) |

CR=complete response; DCR=disease control rate; ORR=objective response rate; PD=progressive disease; PR-partial response; SD=stable disease; TPS=tumor proportion score.
Database Cutoff Date: 07-NOV-2016

The combination regimen was tolerable for subjects. Adverse events were reported in 42 (98%) of the 45 subjects who received pembrolizumab 2 mg/kg plus ipilimumab 1 mg/kg; the most frequent AE was fatigue (44%). Twenty-two (49%) of these subjects experienced Grade 3 to 5 AEs, the most frequent of which was fatigue, and syncope (7% each). The toxicity was manageable. Eleven (24%) subjects discontinued treatment because of AEs. There was one treatment-related death from pancreatitis. While the dataset for the regimen combining pembrolizumab and ipilimumab is small with 44 subjects, the ORR in previously treated subjects with the combination is greater than what would be expected from pembrolizumab monotherapy in a broad population of subjects with NSCLC whose tumors expressed PD-L1 with a TPS ≥1% (18.0% [95% CI: 14.1, 22.5] for pembrolizumab 2 mg/kg in KEYNOTE-010). The addition of ipilimumab to pembrolizumab did not add excessive toxicity in this dose and schedule. These data indicate that the combination regimen of pembrolizumab and ipilimumab may enhance the efficacy of pembrolizumab monotherapy in a first-line setting, without substantially increasing the toxicity. The Sponsor has also conducted a Phase 1b study of pembrolizumab at 2 mg/kg every 3 weeks in combination with ipilimumab at 1 mg/kg Q3W (4 doses) in participants with advanced melanoma (KEYNOTE-029). Results of a melanoma expansion cohort (N=153) showed that the combination was reasonably well tolerated with 38% treatment-related Grade 3 to 4 AEs and highly efficacious with a 57% ORR [31].

The proposed dose and schedule of ipilimumab 1 mg /kg every 6 week to be combined with IV pembrolizumab 200 mg every 3 weeks for the duration of treatment in KEYNOTE-598 is based on open-label, Phase 1, multicohort study CheckMate-012, which evaluated nivolumab plus ipilimumab in previously untreated advanced NSCLC. CheckMate-012 included multiple cohorts with different treatment regimen schedules including 3 cohorts of nivolumab (1-3 mg/kg) every 2 weeks plus ipilimumab (1-3 mg /kg) every 3 weeks for 4

cycles followed by nivolumab monotherapy, and 3 other cohorts with nivolumab (1-3 mg /kg) every 2 weeks plus ipilimumab 1 mg /kg every (6-12) weeks for the duration of treatment. The toxicity observed in the first 3 cohorts, when ipilimumab dosing was every 3 weeks for 4 cycles was high with Grade 3 to 4 TRAEs of (29-58%), and TRAEs leading to discontinuation (13-40%), with 3 reported treatment-related deaths from respiratory failure, pulmonary hemorrhage, and toxic epidermal necrolysis.

The combination of nivolumab 3 mg/kg every 2 weeks plus ipilimumab 1 mg/kg at dosing intervals of every 6 or 12 weeks had manageable toxicity after a median follow-up of approximately 1 year, with Grade 3 to 4 TRAEs occurring in 13 (33%) patients taking nivolumab 3 mg /kg Q2W + ipilimumab 1 mg/kg Q6W and treatment-related AEs leading to discontinuation 5 (13%), with no treatment related death. The most commonly reported Grade 3 to 4 TRAEs were increased lipase (3 [8%] and no patients, respectively), pneumonitis (2 [5%] and 1 [3%] patients), adrenal insufficiency (1 [3%] and 2 [5%] patients), and colitis (1 [3%] and 2 [5%] patients) [29]. The median number of doses in (39 patients) the cohort receiving nivolumab 3mg /kg Q2W + ipilimumab 1mg/kg Q6W was 8 (3−18) doses for nivolumab and 2 (1−6) doses for ipilimumab, with the median duration of therapy 4.1 (1.9–10.1) months for nivolumab, and 3.4 (1.4–9.4) months for ipilimumab. Based on CheckMate-012 findings, the Phase 3 study CheckMate 227 of the combination of nivolumab 3 mg/kg every 2 weeks plus ipilimumab 1 mg/kg every 6 weeks (until PD or discontinuation due to toxicity) was started and is ongoing.

The above overall experience of the ipilimumab dose in combination with PD1 inhibitors, and the assumption of potential additive antitumor activity of ipilimumab when combined with pembrolizumab for the duration of treatment, supports the dose selected for this Phase 3 study of IV ipilimumab 1 mg /kg every 6 weeks to be combined with IV pembrolizumab 200 mg every 3 weeks.

Based on the results of KEYNOTE-024, pembrolizumab monotherapy has become a SOC for treating Stage IV NSCLC in patients with PD-L1 TPS ≥50% with no *EGFR* or *ALK* genomic tumor aberrations. The study resulted in a significant PFS benefit for pembrolizumab over the SOC at the time (platinum-doublet therapy), with an HR of 0.50 (95% CI: 0.37-0.68, p <0.001; median PFS 10.3 months [95% CI: 6.7-not reached] with pembrolizumab and 6.0 months [95% CI: 4.2-6.2] with platinum-doublet), as well as an OS benefit with an HR of 0.60 (95% CI: 0.41-0.89, *p*=0.005; median OS was not reached in either treatment arm) [24]. The results from KEYNOTE-024 established pembrolizumab as first-line therapy for patients whose tumors have a TPS ≥50% and in whom *EGFR* or *ALK*-directed therapies are not indicated; the regimen has received regulatory approval for this use by the FDA and EMA. The use of an ipilimumab matching placebo in combination with pembrolizumab will ensure the objectivity of the local investigators' treatment decision and AE causality assessments, while still providing subjects a SOC treatment.

### 4.2.3 Rationale for Endpoints

#### 4.2.3.1 Efficacy Endpoints

##### 4.2.3.1.1 Primary Endpoints

OS has been recognized as the gold standard for the demonstration of superiority of a new antineoplastic therapy in randomized clinical studies and is a standard assessment of clinical benefit in subjects with metastatic NSCLC.

PFS is an acceptable measure of clinical benefit for a randomized Phase 3 trial that demonstrates superiority of a new antineoplastic therapy, especially if the magnitude of effect is large and the therapy has an acceptable risk-benefit profile. Furthermore, it is an endorsed regulatory endpoint for 1L NSCLC trials with recent FDA approvals of pembrolizumab for the 1L treatment of patients with metastatic NSCLC whose tumors have high PD-L1 positive expression (TPS ≥50%) and no *EGFR* or *ALK* genomic tumor aberrations, and European Medicines Agency (EMA) approvals including the EGFR inhibitors, afatinib and erlotinib. PFS will be assessed per RECIST 1.1 by blinded independent central, which will be blinded to the treatment assignment to minimize any bias in the response assessments.

##### 4.2.3.1.2 Secondary Endpoints

ORR by RECIST 1.1 criteria as assessed by BICR is considered preliminary evidence of efficacy.

DOR based on RECIST 1.1 and assessed by BICR is a commonly accepted endpoint by both regulatory authorities and the oncology community.

Change from baseline in global health status/quality of life score from the EORTC QLQ-C30 (items 29 and 30) is a common PRO endpoint in trials of immunotherapy for advanced NSCLC [32] [33].

TTD in cough, pain in chest, or shortness of breath, defined as the time to the first onset of a 10-point or greater score deterioration from baseline in any one of the 3 symptoms, confirmed by a second adjacent 10-point or greater score deterioration from baseline has been used as an endpoint in advanced NSCLC immunotherapy trials [34] [35].

##### 4.2.3.1.3 Exploratory Endpoints

**NOTE: As of Amendment 06, data for exploratory endpoints are no longer being collected.**

The EORTC QLQ-C30 and EORTC QLQ-LC13 will be used to investigate (1) quality of life and (2) disease- and treatment-related symptoms. They are not pure efficacy or safety endpoints because they are affected by both disease progression and treatment tolerability. The EQ-5D-5L will be used to calculate health utilities for health economic models.

The Non-small Cell Lung Cancer Symptom Assessment Questionnaire (NSCLC-SAQ) will be used to add to existing psychometric analyses of the instrument. The NSCLC-SAQ has been developed in accordance with FDA guidance on patient-reported outcomes (PRO). Results from a quantitative pilot study generated evidence of good item and scale

performance and provided support for the content validity, reliability, and validity of the instrument [36]. These data, along with initial qualitative work [37], were submitted to FDA to support qualification of the NSCLC-SAQ for use in NSCLC clinical trials to measure a patient-reported, symptom-based endpoint.

The PGIC-L PGIS-LC, and PGIC-LC questionnaires will be used to investigate clinically meaningful thresholds for change in the cough, pain in chest, or shortness of breath scales from the EORTC QLQ-LC13/QLQ-C30 and the NSCLC-SAQ total score.

PFS and ORR will be evaluated using modified RECIST 1.1 for immune-based therapeutics (iRECIST) [1], as assessed by the investigator in subjects treated with pembrolizumab plus ipilimumab compared to pembrolizumab plus placebo. RECIST 1.1 will be adapted to account for the unique tumor response characteristics seen following treatment with 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 subjects may manifest a clinical response after an initial increase in tumor burden or even the appearance of new lesions. Standard RECIST 1.1 may, therefore, not provide an accurate response assessment of immunotherapeutic agents such as pembrolizumab. Based on an analysis of subjects with melanoma enrolled in KEYNOTE-001 (KN001), 7% of evaluable subjects experienced delayed or early tumor pseudoprogression. Of note, subjects who had PD by RECIST 1.1 but not by the immune-related response criteria [38] had longer OS than subjects with PD by both criteria [39]. Additionally, the data suggest that RECIST 1.1 may underestimate the benefit of pembrolizumab in approximately 15% of subjects. These findings support the need to apply a modification to RECIST 1.1 that takes into account the unique pattern of atypical responses in immunotherapy and enables treatment beyond initial radiographic progression, if the subject is clinically stable.

Modified RECIST 1.1 for immune-based therapeutics assessment has been developed and published by the RECIST Working Group, with input from leading experts from industry and academia, along with participation from the US FDA and the EMA [1]. It is adapted to account for the unique tumor response seen with immunotherapeutics. The unidimensional measurement of target lesions, qualitative assessment of nontarget lesions, and response categories are identical to RECIST 1.1, until progression is seen by RECIST 1.1. However, if a subject is clinically stable, additional imaging may be performed to confirm radiographic progression. iRECIST will be used by investigators to assess tumor response and progression, and make treatment decisions.

#### 4.2.3.2 Patient-reported Outcomes

**NOTE: As of Amendment 06, PROs will no longer be collected.**

The EORTC QLQ-C30 was developed to assess the quality of life of cancer subjects. It has been translated and validated into 81 languages and used in more than 3,000 studies worldwide. It contains 5 functioning scales (i.e., physical, role, cognitive, emotional, and social), 3 symptom scales (i.e., fatigue, nausea, pain) and additional single symptom items. It is scored on a 4-point scale (1 = not at all, 2 = a little, 3 = quite a bit, 4 = very much). The

EORTC QLQ-C30 instrument also contains 2 global scales that use 7-point scale scoring with anchors (1 = very poor; 7 = excellent).

The EORTC QLQ-LC13, a supplemental lung cancer-specific module, comprises multi-item and single-item measures of lung cancer-associated symptoms (i.e., coughing, hemoptysis, dyspnea, pain) and side-effects from chemotherapy and radiation (i.e., hair loss, neuropathy, sore mouth, dysphagia). It is scored on a 4 point scale (1 = not at all, 2 = a little, 3 = quite a bit, 4 = very much) and has been translated and validated into 64 languages.

The EQ-5D-5L is a standardized instrument for use as a measure of health outcome. The EQ-5D-5L will provide data for use in economic models and analyses including developing health utilities or quality-adjusted life years. The 5 health-state dimensions in this instrument include the following: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension is rated on a five-point scale from 1 (no problem) to 5 (extreme problem or unable to perform).

The NSCLC-SAQ contains 7 items assessing symptoms of metastatic NSCLC (i.e., coughing, pain, dyspnea, fatigue, and reduced appetite). The recall period is 7 days. Each item has a 5-point verbal rating scale from either "No symptom at all" to "Very severe symptom" or from "Never to Always" depending on the item's format (i.e., severity or frequency). A single total symptom score is computed based on item responses.

The PGIC-L and PGIC-LC will be administered to assess change since the last visit in cough, pain in chest, shortness of breath and total lung cancer symptoms, as measured with the EORTC QLQ-C30/ EORTC QLQ-LC13 and the NSCLC-SAQ, respectively. The response options are much better, better, a little better, no change, a little worse, worse, and much worse for the 4 questions in these 2 instruments.

The PGIS-LC will be administered to assess the current severity of overall lung cancer symptoms. The response options for this question are not severe, mildly severe, moderately severe, very severe, and extremely severe.

#### 4.2.3.3 Safety Endpoints

Safety parameters commonly used for evaluating investigational systemic anticancer treatments are included as safety endpoints including, but not limited to, the incidence of, causality, and outcome of AEs/SAEs; and changes in vital signs and laboratory values. AEs will be assessed as defined by CTCAE, Version 4.0.

#### 4.2.3.4 Planned Exploratory Biomarker Research

**Introduction**: Cancer immunotherapies represent an important and novel class of antitumor agents. However, the mechanism of action of these exciting new therapies is not completely understood and much remains to be learned regarding how best to leverage these new drugs in treating patients. Thus, to aid future patients, it is important to investigate the determinants of response or resistance to cancer immunotherapy as well as determinants of AEs in the course of our clinical trials. These efforts will identify novel predictive/pharmacodynamic biomarkers and generate information that will better guide single-agent and combination therapy with immuno-oncology drugs. To identify novel biomarkers, we will collect biospecimens (blood components, tumor material, etc.) to support

analyses of cellular components (e.g., protein, deoxyribonucleic (DNA), RNA, metabolites) and other circulating molecules. Investigations may include but are not limited to:

**Germline (blood) genetic analyses (e.g., single nucleotide polymorphisms analyses, whole exome sequencing, whole genome sequencing):** This research will evaluate whether genetic variation within a clinical trial population correlates with response to the treatment(s) under evaluation. If genetic variation is found to predict efficacy or AEs, the data might inform optimal use of therapies in the patient population. Furthermore, it is important to evaluate germline DNA variation across the genome in order to interpret tumor-specific DNA mutations. Finally, microsatellite instability may be evaluated as this is an important biomarker for some cancers (i.e., colorectal cancer).

**Genetic (DNA) analyses from tumor**: The application of new technologies, such as next generation sequencing, has provided scientists the opportunity to identify tumor-specific DNA changes (e.g., mutations, methylation status, microsatellite instability). Key molecular changes of interest to immune-oncology drug development include (for example) the mutational burden of tumors and the clonality of T-cells in the tumor microenvironment. Increased mutational burden (sometimes referred to as a 'hyper-mutated' state) may generate neo-antigen presentation in the tumor microenvironment. To conduct this type of research, it is important to identify tumor-specific mutations that occur across all genes in the tumor genome. Thus, genome-wide approaches may be used for this effort. Note that in order to understand tumor-specific mutations, it is necessary to compare the tumor genome with the germline genome. Microsatellite instability may also be evaluated as this is an important biomarker for some cancers (i.e., colorectal cancer).

**Tumor and blood RNA analyses**: Both genome-wide and targeted messenger RNA expression profiling and sequencing in tumor tissue and in blood may be performed to define gene signatures that correlate to clinical response to treatment with pembrolizumab or other immunotherapies. Pembrolizumab induces a response in tumors that likely reflects an inflamed/immune phenotype. Specific immune-related gene sets (such as those capturing interferon-gamma transcriptional pathways) may be evaluated and new signatures may be identified. Individual genes related to the immune system may also be evaluated (e.g., IL-10). MicroRNA profiling may also be pursued.

**Proteomics and immunohistochemistry (IHC) using blood or tumor**: Tumor and blood samples from this study may undergo proteomic analyses (e.g., PD-L1 IHC). Programmed death-ligand 1 protein level in tumor sections, assessed by IHC, has been shown to correlate with response to pembrolizumab in patients with NSCLC, and an in vitro diagnostic device has been developed for use with pembrolizumab in NSCLC. Preliminary data indicate that this association may also be true in additional cancer types (i.e., triple-negative breast cancer, head and neck cancer, and gastric cancer). Additional tumor or blood-derived proteins may also correlate with response to pembrolizumab. Therefore, tumor tissue may be subjected to proteomic analyses using a variety of platforms that could include but are not limited to immunoassays, liquid chromatography/mass spectrometry. This approach could identify novel protein biomarkers that could aid in patient selection for pembrolizumab (MK-3475) therapy.

**Other blood-derived biomarkers**: In addition to expression on the tumor tissue, PD-L1 and other tumor-derived proteins can be shed from the tumor and released into the blood. Assays such as enzyme-linked immunoassay measure such proteins in serum. Correlation of expression with response to pembrolizumab therapy may identify new approaches for predictive biomarkers in blood, representing a major advance from today's reliance on assessing tumor biomarkers. This research would serve to develop such assays for future clinical use.

#### 4.2.3.5 Future Biomedical Research

The Sponsor will conduct Future Biomedical Research on specimens consented for future biomedical research during this clinical trial. This research may include genetic analyses (DNA), gene expression profiling (RNA), proteomics, metabolomics (serum, plasma) and/or the measurement of other analytes, depending on which specimens are consented for future biomedical research.

Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol (as part of the main trial) and will only be conducted on specimens from appropriately consented subjects. The objective of collecting/retaining specimens for Future Biomedical Research is to explore and identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments. The overarching goal is to use such information to develop safer, more effective drugs/vaccines, and/or to ensure that subjects receive the correct dose of the correct drug/vaccine at the correct time. The details of this Future Biomedical Research are presented in Section 12.2 – Collection and Management of Specimens for Future Biomedical Research.

### 4.3 Benefit/Risk

**NOTE: The results of IA1 of this study indicated that the study did not meet the prespecified success criteria for improvement in PFS or OS for the combination of pembrolizumab plus ipilimumab compared with pembrolizumab plus placebo. Furthermore, a nonbinding futility analysis was performed at IA1 at the request of the DMC. This analysis showed the study met the criteria for declaring futility and the benefit-risk assessment was not considered positive to continue the trial. Therefore, the benefit-risk assessment of pembrolizumab plus ipilimumab is no longer applicable and has been removed.**

It cannot be guaranteed that subjects in clinical trials will directly benefit from treatment during participation as clinical trials are designed to provide information about the safety and effectiveness of an investigational medicine.

Despite the substantial improvement in PFS and OS observed with pembrolizumab as compared to SOC platinum-doublet chemotherapy in KEYNOTE-024, the clinical outlook of patients with previously untreated metastatic/recurrent NSCLC whose tumors express high levels of PD-L1 can be improved with further gains in cure rates and long-term OS needed. As such, urgency remains to investigate new treatments for this patient population.

Additional details regarding specific benefits and risks for subjects participating in this clinical trial may be found in the accompanying IB and informed consent documents.

# 5.0 METHODOLOGY

## 5.1 Entry Criteria

### 5.1.1 Diagnosis/Condition for Entry into the Trial

Male/female subjects with Stage IV metastatic NSCLC whose tumors are PD-L1 positive (TPS ≥50%), do not harbor *EGFR*-sensitizing mutations and *ALK* translocations that are amenable to treatment with respective tyrosine kinase inhibitor therapy, and who have received no systemic anticancer therapy for their Stage IV metastatic NSCLC will be enrolled in this trial.

### 5.1.2 Subject Inclusion Criteria

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

1. Be willing and able to provide written informed consent for the trial. The subject may also provide consent/assent for FBR; however, the subject may participate in the main trial without participating in FBR.

2. Be at least 18 years of age on the day of signing informed consent.

3. Have a histologically or cytologically confirmed diagnosis of Stage IV metastatic NSCLC (AJCC version 8).

4. Have measurable disease per RECIST 1.1 as assessed by the local site investigator/radiology. Lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesion.

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

6. Have an ECOG Performance Status of 0 or 1.

7. Have adequate organ function as indicated by the following laboratory values in Table 4. Specimens must be collected within 10 days prior to the start of trial treatment.

Table 4 Adequate Organ Function Laboratory Values

| System | Laboratory Value[a] |
|---|---|
| **Hematological** | |
| Absolute neutrophil count | ≥1,500/mcL |
| Platelets | ≥100,000/mcL |
| Hemoglobin | ≥9 g/dL or ≥5.6 mmol/L[b] |
| **Renal** | |
| Serum creatinine OR calculated CrCl[c] (GFR can also be used in place of creatinine or CrCl) | ≤1.5 × upper limit of normal (ULN) **OR** ≥30 mL/min for subjects with creatinine levels >1.5 × institutional ULN |
| **Hepatic** | |
| Total bilirubin | ≤1.5 × ULN OR direct bilirubin ≤ULN for subjects with total bilirubin levels >1.5 × ULN |
| AST (SGOT) and ALT (SGPT) | ≤2.5 × ULN |
| **Coagulation** | |
| INR or PT<br>aPTT or (PTT) | ≤1.5 × ULN unless subject is receiving anticoagulant therapy as long as PT/INR or aPTT/PTT is within therapeutic range of intended use of anticoagulants |

[a] All screening laboratory tests (local) must be reviewed by the investigator or qualified designee and acceptable prior to randomization.
[b] Criteria must be met without erythropoietin dependency and without packed red blood cell transfusion within last 2 weeks.
[c] 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)
Note: This table includes eligibility-defining laboratory value requirements for treatment; laboratory value requirements should be adapted according to local regulations and guidelines for the administration of specific chemotherapies.
Abbreviations: ALT (SGPT)=alanine aminotransferase (serum glutamic pyruvic transaminase); aPPT = activated partial thromboplastin time AST (SGOT)=aspartate aminotransferase (serum glutamic oxaloacetic transaminase); CrCl = creatinine clearance; GFR=glomerular filtration rate; INR = international normalized ratio; PT = prothrombin time; PTT = partial thromboplastin time; ULN=upper limit of normal.

8. Have provided archival tumor tissue sample or newly obtained core or excisional biopsy of a tumor lesion not previously irradiated. Tumor demonstrates PD-L1 expression in ≥50% of tumor cells (TPS ≥50%) as assessed by IHC as determined by an FDA-approved test (22C3 Pharm IHC PharmDx [Dako] assay) at a central laboratory. Formalin-fixed, paraffin-embedded (FFPE) tissue blocks are preferred to slides. Newly obtained biopsies are preferred to archived tissue.

   Note: If submitting unstained cut slides, newly cut slides should be submitted to the testing laboratory within 14 days from the date slides are cut (details pertaining to tumor tissue submission can be found in the Procedures Manual).

9. Female subjects of childbearing potential must have a negative serum pregnancy test within 72 hours prior to receiving the first dose of study medication.

10. A female subject is eligible to participate if she is not pregnant (see Section 12.5), not breastfeeding, and at least one of the following conditions applies: (1) is not considered to be a woman of childbearing potential (WOCBP) as described in Section 12.5 or (2) is a WOCBP who agrees to follow the contraceptive guidance in Section 12.5 during the treatment period and for at least 120 days (corresponding to time needed to eliminate any study treatment(s) (MK and or any active comparator/combination).

11. A male subject must agree to use contraception as detailed in Section 12.5 of this protocol during the treatment period and for at least 120 days after the last dose of study treatment and refrain from donating sperm during this period. **Note: As of amendment 06, contraception is no longer required for male participants. Sperm donation is also acceptable.**

### 5.1.3 Subject Exclusion Criteria

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

1. Has received prior systemic chemotherapy/other targeted or biological antineoplastic therapy treatment for their Stage IV metastatic NSCLC.

   Note: Treatment with chemotherapy and/or radiation as part of neoadjuvant/adjuvant therapy is allowed as long as therapy was completed at least 6 months prior to the diagnosis of metastatic disease.

2. Tumor harbors an *EGFR*-sensitizing (activating) mutation or an *ALK* translocation.

   Note: *EGFR*-sensitizing mutations are those mutations that are amenable to treatment with tyrosine kinase inhibitors including erlotinib, gefitinib, or afatinib. Subjects with nonsquamous histologies will not be randomized until *EGFR* mutation status and/or ALK translocation status is available in source documentation at the site.

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

3. Is currently participating in or has participated in a trial of an investigational agent or has used an investigational device within 4 weeks prior to the first dose of trial treatment.

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

4. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti PD-L2 agent or with an agent directed to another stimulatory or coinhibitory T-cell receptor (eg, CTLA-4, OX-40, CD137).

5. Has received prior radiotherapy within 2 weeks of start of trial treatment or received lung radiation therapy of >30 Gy within 6 months of the first dose of trial treatment. Subjects

must have recovered from all radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis. A 1-week washout is permitted for palliative radiation (≤2 weeks of radiotherapy) to non-CNS disease.

6. The subject's NSCLC can be treated with curative intent with surgical resection, localized radiotherapy, or chemoradiation.

   Note: If subject received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting trial treatment.

7. Tumor specimen is not evaluable for PD-L1 expression.

8. Is receiving systemic steroid therapy ≤7 days prior to the first dose of trial treatment or receiving any other form of immunosuppressive medication.

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

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

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

9. Has a known additional malignancy that is progressing or has required active treatment within the past 3 years.

   Note: Subjects with basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or carcinoma in situ (e.g., breast carcinoma, cervical cancer in situ) that have undergone potentially curative therapy are not excluded.

10. Has known untreated–CNS metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are radiologically stable (i.e., without evidence of progression for at least 4 weeks by repeat imaging [note that the repeat imaging should be performed during study screening]), clinically stable, and without requirement of steroid treatment for at least 14 days prior to first dose of trial treatment.

11. Has an 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, physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment and is allowed.

12. Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (i.e., doses exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior the first dose of trial drug.

13. Has a history of (noninfectious) pneumonitis that required systemic steroids or current pneumonitis/interstitial lung disease.

14. Has had an allogeneic tissue/solid organ transplant.

15. Has received a live vaccine within 30 days prior to the first dose of trial treatment. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, Bacillus Calmette-Guérin (BCG), and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g., FluMist®) are live attenuated vaccines and are not allowed.

16. Has an active infection requiring systemic therapy.

17. Has a known history of HIV infection. No HIV testing is required unless mandated by local health authority.

18. Has a known history of hepatitis B (defined as hepatitis B surface antigen [HBsAg] reactive) or known active hepatitis C virus (defined as hepatitis C virus (HCV) RNA [qualitative] is detected) infection.

    Note: no testing for hepatitis B and hepatitis C is required unless mandated by local health authority.

19. Has a known history of active tuberculosis (TB; *Bacillus Tuberculosis*).

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

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

22. 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).

23. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the Screening Visit (Visit 1) through 120 days after the last dose of pembrolizumab or 90 days after the last dose of ipilimumab.

24. Has severe hypersensitivity (≥ Grade 3) to pembrolizumab and/or any of its excipients and/or to ipilimumab and/or any of its excipients.

25. Subjects with known *ROS1* mutation: if treatment and testing for *ROS1* is approved and accessible.

## 5.2 Trial Treatment(s)

**NOTE: As of Amendment 06, ipilimumab and matching placebo have been removed from the study. This section has been updated accordingly.**

The treatment(s) to be used in this trial are outlined below in Table 5.

Table 5 Trial Treatment

| Trial Treatment Name | Dosage Formulation | Unit Dose Strength(s) | Dosage Level(s) | Route of Administration | Sourcing |
|---|---|---|---|---|---|
| Pembrolizumab | Solution for Infusion | 25 mg / mL | 200 mg Q3W | IV infusion | Central |

Abbreviations: IV=intravenous; NA=not applicable; Q3W=every 3 weeks.

Trial treatment must begin as close to treatment allocation/randomization as possible but no more than three days later.

All trial treatments will be administered on an outpatient basis.

All supplies indicated in Table 5 above will be provided centrally by the Sponsor or locally by the trial site, subsidiary or designee, depending on local country operational or regulatory requirements.

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

Details on the dose calculation, preparation, and administration are provided in the Pharmacy Manual.

Pembrolizumab will be administered as per the approved product labels.

The rationale for selection of doses to be used in this trial is provided in Section 4.0 – Background & Rationale. There are no specific calculations or evaluations required to be performed in order to administer the proper dose to each subject.

#### 5.2.1.2 Dose Modification (Escalation/Titration/Other) and Toxicity Management

**NOTE: As of Amendment 06, text in this section relating to dose modification of ipilimumab/matching placebo is no longer applicable. This section has been updated accordingly.**

**Pembrolizumab:**

Dose increase or decrease of pembrolizumab will not be permitted in individual subjects. If a dose of pembrolizumab is withheld for toxicity, then subjects may resume dosing, if appropriate, at their next scheduled appointment or when toxicity has improved as described in Table 6 below.

AEs (both nonserious and serious) observed may occur shortly after the first dose through 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 6 below. See Section 5.6 – Rescue Medications & Supportive Care for supportive care guidelines, including use of corticosteroids.

In addition, subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures, as described in Section 5.6.1 – Supportive Care Guidelines, are also included in Table 6.

AEs associated with pembrolizumab exposure may represent an immunologic etiology. These immune-related AEs (irAEs) may occur shortly after the first dose through several months after the last dose of treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical trial data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, or skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab and administer corticosteroids. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab are provided in Table 6.

Table 6 Dose Modification and Toxicity Management Guidelines for Immune-related AEs Associated with Pembrolizumab or Previously-Administrated Ipilimumab

| **Immune-related AEs** | **Toxicity Grade or Conditions (CTCAEv4.0)** | **Action Taken to Pembrolizumab** | **irAE Management with Corticosteroid and/or Other Therapies** | **Monitor and Follow-up** |
|---|---|---|---|---|
| Pneumonitis | Grade 2 | Withhold | • Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper | • Monitor subjects for signs and symptoms of pneumonitis<br>• Evaluate subjects with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment<br>• Add prophylactic antibiotics for opportunistic infections |
| | Grade 3 or 4, or recurrent Grade 2 | Permanently discontinue | | |
| Diarrhea/colitis | Grade 2 or 3 | Withhold | • Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper | • Monitor subjects for signs and symptoms of enterocolitis (i.e. diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (i.e. peritoneal signs and ileus).<br>• Subjects with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis.<br>• Subjects with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion. |
| | Grade 4 | Permanently discontinue | | |
| AST/ALT elevation or Increased Bilirubin | Grade 2 | Withhold | • Administer corticosteroids (initial dose of 0.5- 1 mg/kg prednisone or equivalent) followed by taper | • Monitor with liver function tests (consider weekly or more frequently) until liver enzyme value returned to baseline or is stable |
| | Grade 3 or 4 | Permanently discontinue | • Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper | |

| Immune-related AEs | Toxicity Grade or Conditions (CTCAEv4.0) | Action Taken to Pembrolizumab | irAE Management with Corticosteroid and/or Other Therapies | Monitor and Follow-up |
|---|---|---|---|---|
| Type 1 diabetes mellitus (T1DM) or Hyperglycemia | Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure | Withhold | • Initiate insulin replacement therapy for subjects with T1DM<br>• Administer antihyperglycemic in subjects with hyperglycemia | • Monitor subjects for hyperglycemia or other signs and symptoms of diabetes |
| Hypophysitis | Grade 2 | Withhold | • Administer corticosteroids and initiate hormonal replacements as clinically indicated | • Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency) |
| | Grade 3 or 4 | Withhold or permanently discontinue[a] | | |
| Hyperthyroidism | Grade 2 | Continue | • Treat with nonselective beta-blockers (e.g. propranolol) or thionamides as appropriate | • Monitor for signs and symptoms of thyroid disorders |
| | Grade 3 or 4 | Withhold or permanently discontinue[a] | | |
| Hypothyroidism | Grade 2-4 | Continue | • Initiate thyroid replacement hormones (e.g. levothyroxine or liothyronine) per standard of care | • Monitor for signs and symptoms of thyroid disorders. |
| Nephritis and renal dysfunction | Grade 2 | Withhold | • Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper | • Monitor changes of renal function |
| | Grade 3 or 4 | Permanently discontinue | | |
| Myocarditis | Grade 1 or 2 | Withhold | • Based on severity of AE administer corticosteroids | • Ensure adequate evaluation to confirm etiology and/or exclude other causes |
| | Grade 3 or 4 | Permanently discontinue | | |

| Immune-related AEs | Toxicity Grade or Conditions (CTCAEv4.0) | Action Taken to Pembrolizumab | irAE Management with Corticosteroid and/or Other Therapies | Monitor and Follow-up |
|---|---|---|---|---|
| All Other immune-related AEs | Intolerable/ persistent Grade 2 | Withhold | • Based on type and severity of AE administer corticosteroids | • Ensure adequate evaluation to confirm etiology or exclude other causes |
| | Grade 3 | Withhold or discontinue based on the type of event. Events that require discontinuation include but not limited to: Guillain-Barre Syndrome, encephalitis, Stevens-Johnson Syndrome and toxic epidermal necrolysis | | |
| | Grade 4 or recurrent Grade 3 | Permanently discontinue | | |

[a] Withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician.

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

**General Instructions:**

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

Abbreviations: AEs=adverse events; ALT (SGPT)=alanine aminotransferase (serum glutamic pyruvic transaminase); AST (SGOT)=aspartate aminotransferase (serum glutamic oxaloacetic transaminase); CTCAE=Common Terminology Criteria for Adverse Events; DKA=diabetic ketoacidosis; GI = gastrointestinal; IV=intravenous; irAE=immune-related adverse events; T1DM=Type 1 diabetes mellitus

Pembrolizumab may cause severe or life threatening infusion-reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab associated infusion reaction are provided in Table 7.

Table 7 Pembrolizumab Infusion Reaction Dose Modification and Treatment Guidelines

| NCI CTCAE Grade | Treatment | Premedication at Subsequent Dosing |
|---|---|---|
| **Grade 1**<br>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**<br>Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hours | **Stop Infusion.**<br>Additional appropriate medical therapy may include but is not limited to:<br>IV fluids<br>Antihistamines<br>NSAIDs<br>Acetaminophen<br>Narcotics<br>Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.<br>If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g. from 100 mL/hr to 50 mL/hr); otherwise dosing will be withheld until symptoms resolve and the subject should be premedicated for the next scheduled dose.<br>**Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further treatment with pembrolizumab.** | Subject may be premedicated 1.5 h (± 30 minutes) prior to infusion of pembrolizumab with:<br>Diphenhydramine 50 mg po (or equivalent dose of antihistamine).<br>Acetaminophen 500-1000 mg po (or equivalent dose of analgesic). |

| NCI CTCAE Grade | Treatment | Premedication at Subsequent Dosing |
|---|---|---|
| **Grades 3 or 4**<br>Grade 3:<br>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)<br>Grade 4:<br>Life-threatening; pressor or ventilatory support indicated | **Stop Infusion.**<br>Additional appropriate medical therapy may include but is not limited to:<br>Epinephrine**<br>IV fluids<br>Antihistamines<br>NSAIDs<br>Acetaminophen<br>Narcotics<br>Oxygen<br>Pressors<br>Corticosteroids<br>Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.<br>Hospitalization may be indicated.<br>**In cases of anaphylaxis, epinephrine should be used immediately.<br>**Subject is permanently discontinued from further treatment with pembrolizumab.** | No subsequent dosing |
| Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration.<br>For further information, please refer to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE) at http://ctep.cancer.gov | | |

Abbreviations: CTCAE=Common Terminology Criteria for Adverse Events; IV=intravenous; NCI=National Cancer Institute; NSAIDs=nonsteroidal anti-inflammatory drugs; PO=oral.

**Other Allowed Dose Interruption for Pembrolizumab**

Pembrolizumab may be interrupted for situations other than treatment-related AEs such as medical/surgical events or logistical reasons not related to study therapy. Subjects should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the patient's study record.

### 5.2.2 Timing of Dose Administration

**NOTE: As of Amendment 06, ipilimumab and matching placebo are removed from the study. This section has been updated accordingly.**

Trial treatment may be administered up to 3 days after randomization for Cycle 1, Day 1 due to administrative reasons. After Cycle 1, there is a 3-day window for all trial treatment administration.

The specific time of pembrolizumab infusion (e.g., time of the week for first administration; time of the day for each administration) should be taken into consideration for study visit procedures.

All trial treatments will be administered on an outpatient basis.

**Pembrolizumab**: 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).

The Pharmacy Manual contains specific instructions for pembrolizumab dose calculation, preparation of the infusion fluid, and administration.

### 5.2.3 Trial Blinding

**NOTE: As of Amendment 06, blinding is no longer applicable as ipilimumab and matching placebo have been removed from the study. Subjects who remain on treatment will receive open-label pembrolizumab monotherapy as per protocol. This section is no longer applicable.**

A double-blinding technique will be used. Ipilimumab and placebo will be prepared and/or dispensed in a blinded fashion by an unblinded pharmacist or qualified trial site personnel. The subject and the investigator who is involved in the treatment administration or clinical evaluation of the subjects are unaware of the group assignments.

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

See Section 7.1.4.2, Blinding/Unblinding, for a description of the method of unblinding a subject during the trial, should such action be warranted.

## 5.3 Randomization or Treatment Allocation

**NOTE: As of Amendment 06, ipilimumab and matching placebo have been removed from the study and no further subjects will be randomized in the study. This section is no longer applicable.**

Treatment allocation/randomization will occur centrally using an interactive voice response system / integrated web response system (IVRS/IWRS). There are 2 treatment arms. Subjects will be assigned randomly in a 1:1 ratio to pembrolizumab plus ipilimumab or pembrolizumab plus placebo, respectively.

## 5.4 Stratification

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

1. ECOG Performance Status: 0 versus 1.
2. Geography: East Asia versus non-East Asia.
3. Predominant tumor histology: squamous versus nonsquamous.

East Asians have a better prognosis than other ethnic groups regarding NSCLC. It is well established that the higher a subject's ECOG Performance Status, the worse his/her prognosis.

## 5.5 Concomitant Medications/Vaccinations (Allowed & Prohibited)

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

### 5.5.1 Acceptable Concomitant Medications

Treatment of complications or AEs, or therapy to ameliorate symptoms (including blood products, blood transfusions, fluid transfusions, antibiotics, and antidiarrheal drugs), may be given at the discretion of the investigator, unless it is expected to interfere with the evaluation of (or to interact with) the study intervention. Antiemetic or any other prophylaxis should be considered in accordance with institutional guidelines. The following concomitant medications are also allowed:

- Hormone replacement therapy (HRT)
- Thyroid hormone suppressive therapy
- Anti-inflammatory agents
- Bisphosphonates or denosumab

All concomitant medications received within 30 days before the first dose of trial treatment through the Safety Follow-up Visit should be recorded. After the Safety Follow-up Visit, record all medications taken for SAEs and ECIs as defined in Section 7.2 – Assessing and Recording Adverse Events. If a subject enters into second course therapy, all concomitant medications received within 30 days before the first dose of second course treatment should be recorded. Following second course therapy Safety Follow-up Visit, record all medications taken for SAEs and ECIs as defined in Section 7.2 – Assessing and Recording Adverse Events.

### 5.5.2 Prohibited Concomitant Medications and/or Treatments

**NOTE: As of Amendment 06, ipilimumab and matching placebo have been removed from the study. This section has been updated accordingly.**

Subjects are prohibited from receiving the following therapies during the screening, treatment, and second course phases 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
- Oncologic surgery for tumor control

- Radiation therapy to RECIST 1.1-defined target disease

  Note: Palliative radiotherapy is permitted for nontarget lesions if considered medically necessary by the treating physician. Please note, for continuation of treatment beyond progression per RECIST 1.1, clinical stability criteria per Section 12.4 must be met, including the no requirement for radiation. Trial therapy should be held during the course of palliative radiotherapy and should be resumed no earlier than the next scheduled administration of trial therapy.

- 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, varicella/zoster (chicken pox), yellow fever, seasonal flu (that contain a live virus), rabies, BCG, and typhoid vaccine.

- Glucocorticoids for any purpose other than to modulate symptoms from an AE, SAE, or for use as a premedication in subjects with a known history of an IV contrast allergy administered as part of computed tomography (CT) radiography. Replacement doses of steroids (for example, prednisone 5 to 7.5 mg daily) are permitted while on study, as is the use of local steroids and the use of inhaled steroids for the control of asthma.

Subjects who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from treatment but continue in the trial for assessment of disease status and survival.

Subjects may receive other medications that the investigator deems to be medically necessary.

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

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

## 5.6 Rescue Medications & Supportive Care

### 5.6.1 Supportive Care Guidelines

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined along with the dose modification guidelines in Section 5.2.1.2 – Dose Modification (Escalation/Titration/Other), (Table 6). Where appropriate, these guidelines include the use of oral or IV treatment with corticosteroids, as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab or previously-administered ipilimumab.

Note: If after the evaluation of the event, it is determined not to be related to pembrolizumab or previously-administered ipilimumab, the investigator does not need to follow the treatment

guidance. Refer to Table 6 in Section 5.2.1.2 – Dose Modification (Escalation/Titration/Other) for guidelines regarding dose modification and supportive care.

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

## 5.7 Diet/Activity/Other Considerations

### 5.7.1 Diet

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

### 5.7.2 Contraception

Pembrolizumab may have adverse effects on a fetus in utero. Refer to Section 12.5 for approved methods of contraception.

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study, subjects of childbearing potential must adhere to the contraception requirement (Section 12.5) from the day of study medication initiation (or 14 days prior to the initiation of study medication for oral contraception) throughout the study period up to 120 days after the last dose of study 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 study.

### 5.7.3 Pregnancy

If a subject inadvertently becomes pregnant while on treatment with pembrolizumab, the subject will be immediately discontinued from study treatment. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the Sponsor without delay and within 24 hours if the outcome is a serious adverse experience (eg, 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 must be reported to the Sponsor and followed as described in Section 7.2.2 – Reporting of Pregnancy and Lactation to the Sponsor.

### 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 breastfeeding are not eligible for enrollment.

## 5.8 Subject Withdrawal/Discontinuation Criteria

### 5.8.1 Discontinuation of Treatment

**NOTE: As of Amendment 06, ipilimumab and matching placebo have been removed from the study. This section has been updated accordingly.**

Discontinuation of treatment does not represent withdrawal from the trial.

As certain data on clinical events beyond treatment discontinuation may be/are important to the study, they must be collected through the subject's last scheduled follow-up, even if the subject has discontinued treatment. Therefore, all subjects who discontinue trial treatment prior to completion of the treatment period will still continue to participate in the trial as specified in Section 6.0 – Trial Flow Chart and Section 7.1.5.6 – Discontinued Subjects Continuing to be Monitored in the Trial.

Subjects may discontinue treatment at any time for any reason or be dropped from treatment at the discretion of the investigator should any untoward effect occur. In addition, a subject may be discontinued from treatment by the investigator or the Sponsor if treatment is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding procedures to be performed at treatment discontinuation are provided in Section 7.1.4 – Other Procedures.

A subject must be discontinued from treatment but continue to be monitored in the trial for any of the following reasons:

- The subject or subject's legally acceptable representative requests to discontinue treatment.
- BICR-verified radiographic disease progression as outlined in Section 7.1.2.6.5 (exception if the Sponsor approves treatment continuation or investigator is awaiting radiographic disease progression confirmation by – iRECIST Assessment of Disease as outlined in Section 7.1.2.6.6)
- Unacceptable adverse experiences as described in Section 7.2 – Assessing and Recording Adverse Events and Section 5.2.1.2 – Dose Modification (Escalation/Titration/Other)
- Any progression or recurrence of any malignancy, or occurrence of another malignancy that requires active treatment
- Intercurrent illness other than another malignancy as noted above that prevents further administration of treatment
- Recurrent Grade 2 pneumonitis
- A confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements
- Investigator's decision to withdraw the subject
- Completion of 35 treatments (approximately 2 years) with pembrolizumab. Note: The number of treatments is calculated starting with the first dose. Subjects who stop after receiving 35 doses of pembrolizumab may be eligible for retreatment if they progress

after stopping trial treatment provided they meet the requirements detailed in Section 7.1.5.6 – Second Course Phase.

- The subject is lost to follow-up
- Administrative reasons

If a subject attains an investigator-assessed confirmed CR by RECIST 1.1, has been treated for at least 8 cycles with pembrolizumab, and received at least 2 treatments with pembrolizumab beyond the date when the initial CR was declared, the subject and investigator may consider stopping therapy with pembrolizumab. Subjects who discontinue therapy after attaining a confirmed CR (or have experienced a CR, PR or stable disease (SD) after 35 administrations of therapy) and then experience radiographic disease progression according to RECIST 1.1 will be eligible for retreatment with pembrolizumab in the Second Course Phase at the discretion of the investigator as described in Section 7.1.5.6 – Second Course Phase. Subjects who discontinue therapy due to a PR and/or SD after 35 trial treatments should follow procedures as scheduled in the End of Treatment Phase of the study and then move to the Follow-up Phase of the study and have assessments performed as indicated in Section 6.0 – Trial Flow Chart.

After the end of treatment, each subject will be followed for a minimum of 30 days for AE monitoring. Serious AEs will be collected for up to 90 days following cessation of treatment or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, as described in Section 7.2.3.1 – Serious Adverse Events. Subjects will have post-treatment follow-up for disease status every 9 weeks until disease progression and every 2 months after disease progression.

### 5.8.2 Pembrolizumab End of Treatment Follow-up

**NOTE: As of Amendment 06, ipilimumab and matching placebo have been removed from the study. This section has been updated accordingly.**

Discontinuation of treatment may be considered for subjects who have attained a confirmed CR and have been treated for at least 8 cycles (at least 24 weeks), and receive at least 2 doses of pembrolizumab beyond the date when the initial CR was declared.

Subjects who have completed 35 cycles of initial treatment with SD, PR, or CR or who stop pembrolizumab early due to CR may be eligible for up to 1 year (17 cycles) of pembrolizumab if they experience disease progression after stopping pembrolizumab treatment. This retreatment is termed the Second Course Phase (Retreatment) and is described in detail in Section 7.1.5.6 – Second Course Phase.

A subject may discontinue treatment for any of the reasons outlined in Section 5.8.1 – Discontinuation of Treatment; however, they will remain in the trial for post-treatment observation for disease status until disease progression, initiating a nonstudy cancer treatment, withdrawing consent, becoming lost to follow-up or entering the Second Course Phase. After documented disease progression and/or cessation of treatment with pembrolizumab, each subject will be followed for OS until death.

For subjects who are discontinued from treatment but continue to be monitored in the trial, see Section 6.0 – Trial Flow Chart, and Section 7.1.5.7 – Discontinued Subjects Continuing to be Monitored in the Trial for those procedures to be completed at each specified visit.

Discontinuation from treatment is "permanent." Once a subject is discontinued, he/she shall not be allowed to restart treatment except as described in Section 7.1.5.6 – Second Course Phase.

### 5.8.3 Withdrawal from the Trial

A subject must be withdrawn from the trial if the subject or subject's legally acceptable representative withdraws consent from the trial.

If a subject withdraws from the trial, they will no longer receive treatment or be followed at scheduled protocol visits.

Specific details regarding procedures to be performed at the time of withdrawal from the trial including the procedures to be performed should a subject repeatedly fail to return for scheduled visits and/or if the study site is unable to contact the subject, as well as specific details regarding withdrawal from Future Biomedical Research are outlined in Section 7.1.4 – Other Procedures.

## 5.9 Subject Replacement Strategy

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

## 5.10 Beginning and End of the Trial

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

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

## 5.11 Clinical Criteria for Early Trial Termination

The clinical trial may be terminated early if the extent (incidence and/or severity) of emerging effects/clinical endpoints is such that the risk/benefit ratio to the trial population as a whole is unacceptable. In addition, further recruitment in the trial or at (a) particular trial site(s) may be stopped due to insufficient compliance with the protocol, Good Clinical Practice (GCP) and/or other applicable regulatory requirements, procedure-related problems or the number of discontinuations for administrative reasons is too high.

## 6.0 TRIAL FLOW CHART

### 6.1 Treatment and Follow-up Phase

**NOTE: As of Amendment 06, ipilimumab and matching placebo have been removed from the study. Subjects who remain on treatment will receive open-label pembrolizumab monotherapy as per protocol. Study procedures have been simplified. The Trial Flow Chart has been amended and assessments no longer required have been deleted.**

| Activity | Screening (Visit 1) | Treatment Period[a] | | | | | | | | | | | | | End of Treatment Phase | | Follow-up Phase | | | Survival Follow-up |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | | | | | | | 1 | 2 | Every 3 Months after Visit 2 | Every 12 weeks or as directed by the Sponsor[b] |
| **Treatment Cycle/ Scheduled Time** | -30 to -1 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 and beyond | Discontinuation Visit | Safety Follow-up Visit | Follow-up Visit 1 | Follow-up Visit 2 | Follow- up Visit 3 and beyond | Survival Follow-up Visit 1 and beyond |
| **Scheduling Window (Days):** | | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | At study drug discontinuation ±3 | 30 Days from last dose ±3 | ±7 Days | ±7 Days | ±7 Days | ±14 Days |
| **Administrative Procedures** | | | | | | | | | | | | | | | | | | | | |
| Informed Consent | X | | | | | | | | | | | | | | | | | | | |
| Informed Consent for FBR (optional)[c] | X | | | | | | | | | | | | | | | | | | | |
| Inclusion/Exclusion Criteria | X | | | | | | | | | | | | | | | | | | | |
| Subject Identification Card | X | | | | | | | | | | | | | | | | | | | |
| Demographics and Medical History | X | | | | | | | | | | | | | | | | | | | |
| Review Prior and Concomitant Medications | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | | | |
| NSCLC Disease Details and Prior Treatment | X | | | | | | | | | | | | | | | | | | | |
| Subsequent Antineoplastic Therapy Status | | | | | | | | | | | | | | | X | X | X | X | X | X |
| Survival Status[b] | | <---------- > | | | | | | | | | | | | | | | | | | X |

| Activity | Screening (Visit 1) | Treatment Period[a] | | | | | | | | | | | | | End of Treatment Phase | | Follow-up Phase | | | Survival Follow-up |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | | | | | | | 1 | 2 | Every 3 Months after Visit 2 | Every 12 weeks or as directed by the Sponsor[b] |
| **Treatment Cycle/ Scheduled Time** | -30 to -1 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 and beyond | Discontinuation Visit | Safety Follow-up Visit | Follow-up Visit 1 | Follow-up Visit 2 | Follow- up Visit 3 and beyond | Survival Follow-up Visit 1 and beyond |
| **Scheduling Window (Days):** | | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | At study drug discontinuation ±3 | 30 Days from last dose ±3 | ±7 Days | ±7 Days | ±7 Days | ±14 Days |
| **Clinical Procedures/Assessments** | | | | | | | | | | | | | | | | | | | | |
| Review AEs | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Full Physical Examination | X | | | | | | | | | | | | | | | | | | | |
| Directed Physical Examination | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | |
| Vital Signs and Weight[d] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | |
| 12-Lead ECG | X | | | | | | | | | | | | | | | | | | | |
| ECOG Performance Status | X | X[e] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | |
| **Study Drug Administration** | | | | | | | | | | | | | | | | | | | | |
| Pembrolizumab | | X | X | X | X | X | X | X | X | X | X | X | X | X | | | | | | |
| **Local Laboratory Procedures/Assessments** | | | | | | | | | | | | | | | | | | | | |
| Pregnancy Test Serum β-hCG[i] | X | | | | | | | | | | | | | | | | | | | |
| PT/INR and aPTT[j] | X[k] | | | | | | | | | | | | | | | | | | | |
| CBC with Differential[l,m] | X[k] | | X | X | X | X | X | X | X | X | X | X | | X[l] | X | X | X | X | | |
| Comprehensive Chemistry Panel[l,m] | X[k] | | X | X | X | X | X | X | X | X | X | X | | X[l] | X | X | X | X | | |
| Urinalysis[m,n] | X[k] | | | | | X | | | | X | | | | X[n] | X | X | | | | |
| TSH, FT3/T3, FT4/T4[m,o] | X[k] | | | X | | X | | X | | X | | X | | X[p] | X | X | | | | |
| ACTH[m] | X[k] | | | X | | X | | X | | X | | X | | X[p] | X | X | | | | |
| ALK Translocation Testing | X | | | | | | | | | | | | | | | | | | | |

| Activity | Screen-ing (Visit 1) | Treatment Period[a] | | | | | | | | | | | | | End of Treatment Phase | | Follow-up Phase | | | Survival Follow-up |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | | | | | | | 1 | 2 | Every 3 Months after Visit 2 | Every 12 weeks or as directed by the Sponsor[b] |
| **Treatment Cycle/ Scheduled Time** | -30 to -1 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 and beyond | Discon-tinuation Visit | Safety Follow-up Visit | Follow-up Visit 1 | Follow-up Visit 2 | Follow- up Visit 3 and beyond | Survival Follow-up Visit 1 and beyond |
| **Scheduling Window (**Days**):** | | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | At study drug discontin-uation ±3 | 30 Days from last dose ±3 | ±7 Days | ±7 Days | ±7 Days | ±14 Days |
| EGFR Mutation Testing | X | | | | | | | | | | | | | | | | | | | |
| **Efficacy Measurements** | | | | | | | | | | | | | | | | | | | | |
| Tumor Imaging[q] | X | | | | X | | | X | | | X | | | X | X | X | X | X | X | |
| **Tumor Biopsies/Archival Tissue Collection** | | | | | | | | | | | | | | | | | | | | |
| Tumor Tissue Collection for PD-L1 Expression | X | | | | | | | | | | | | | | | | | | | |

[a] In general, assessments/procedures are to be performed on Day 1 and prior to the first dose of trial treatment for each cycle unless otherwise specified. Treatment cycles are 3 weeks (21 days). If treatment cycles are adjusted, all procedures except imaging will be completed according to the cycle number and not based on weeks on treatment; imaging will be performed every 9 weeks (63 days ± 7 days) from the date of randomization through 54 weeks, then every 12 weeks (84 days ±7 days) subsequently regardless of any treatment delays.

[b] After verification of disease progression by BICR or the start of new anticancer treatment; contacts are approximately every 12 weeks by telephone. Updated survival status may be requested by the Sponsor at any time during the course of the study. Upon Sponsor notification, all subjects who do not/will not have a scheduled study visit or study contact during the Sponsor defined time period will be contacted for their survival status (excluding subjects that have a death event previously recorded).

[c] This sample should be drawn for planned analysis of the association between genetic variants in DNA and drug response. This sample will not be collected at that site if there is either a local law or regulation prohibiting collection, or if the IRB/IEC does not approve the collection of the sample for these purposes. If the sample is collected, leftover extracted DNA will be stored for FBR if the participant signs the FBR consent. If the planned genetic analyses are not approved, but FBR is approved and consent is given, this sample will be collected for the purpose of FBR.

[d] Vital signs to include temperature, pulse, respiratory rate, weight, and blood pressure. Height will be measured at screening only.

[e] ECOG assessment for eligibility needs to be performed within 7 days of the first dose of trial treatment but before randomization.

[i] For women of reproductive potential, a serum pregnancy test will be performed within 72 hours prior to the first dose. Serum pregnancy test should be repeated if required by local guidelines.

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

[k] Laboratory tests for screening are to be performed within 10 days prior to the first dose of trial treatment.

[l] CBC with differentials and chemistry will be performed every cycle up to Cycle 11, then thereafter at Cycle 13, Cycle 15 etc.

[m] After Cycle 1, laboratory samples can be collected up to 7 days prior to the scheduled time point. Laboratory results must be known and acceptable prior to dosing, except

| Activity | Screen-ing (Visit 1) | Treatment Period[a] | | | | | | | | | | | | | End of Treatment Phase | | Follow-up Phase | | | Survival Follow-up |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | | | | | | | 1 | 2 | Every 3 Months after Visit 2 | Every 12 weeks or as directed by the Sponsor[b] |
| **Treatment Cycle/ Scheduled Time** | -30 to -1 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 and beyond | Discon-tinuation Visit | Safety Follow-up Visit | Follow-up Visit 1 | Follow-up Visit 2 | Follow- up Visit 3 and beyond | Survival Follow-up Visit 1 and beyond |
| **Scheduling Window (**Days**):** | | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | At study drug discontin-uation ±3 | 30 Days from last dose ±3 | ±7 Days | ±7 Days | ±7 Days | ±14 Days |

endocrine testing which must be reviewed prior to the next dose of treatment.
[n] Perform every 4 cycles.
[o] FT3/T3 and FT4/T4 are only required if TSH is out of the normal range.
[p] Perform TSH, FT3/T3, and FT4/T4 testing every other cycle from 13 onward (13, 15, 17, etc.), and ACTH as clinically indicated.
[q] Details are provided in the Site Imaging Manual and Section 7.1.2.6.
Abbreviations: ACTH=adrenocorticotropic hormone; AE=adverse event; ALK=anaplastic lymphoma kinase; aPTT/PTT=Activated Prothrombin Time/Partial thromboplastin time; BICR=blinded independent central review; β-hCG=beta-human chorionic gonadotropin; CBC=complete blood count; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EGFR=epidermal growth factor receptor; 5-level Questionnaire; FBR=Future Biomedical Research; FT3=Free triiodothyronine; FT4=Free thyroxine; NSCLC=nonsmall cell lung cancer; PD-L1=programmed cell death protein-1; PT/INR=Prothrombin Time/International Normalized Ratio; TSH=thyroid stimulating hormone.

## 6.2 Second Course Treatment

**NOTE: As of Amendment 06, ipilimumab and matching placebo have been removed from the study. Subjects who enter Second Course treatment will receive open-label pembrolizumab monotherapy as per protocol. The Trial Flow Chart has been revised accordingly.**

| Activity | Second Course Treatment Cycles[a] | | | | | | | | | | | | | End of Second Course Treatment | | Follow-up | | | Survival Follow-up |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | | | | | | 1 | 2 | Every 3 Months after Visit 2 | Every 12 weeks or as directed by the Sponsor[b] |
| **Treatment Cycle/ Scheduled Time** | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 and beyond | Discontinuation Visit | Safety Follow-up Visit | Follow-up Visit 1 | Follow-up Visit 2 | Follow-up Visit 3 and Beyond | Survival Follow-up Visit 1 and Beyond |
| **Scheduling Window (Days):** | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | At study drug discontinuation ±3 | 30 days from last dose ±3 | ±7 days | ±7 days | ±7 days | ±14 days |
| **Administrative Procedures** | | | | | | | | | | | | | | | | | | | |
| Eligibility Criteria | X | | | | | | | | | | | | | | | | | | |
| Concomitant Medications | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | | | |
| Subsequent Antineoplastic Therapy Status | | | | | | | | | | | | | | X | X | X | X | X | X |
| Survival Status[b] | <---------- | | | | | | | | | | | | | | | | | | X |
| **Study Drug Administration** | | | | | | | | | | | | | | | | | | | |
| Pembrolizumab | X | X | X | X | X | X | X | X | X | X | X | X | X | | | | | | |
| **Clinical Procedures/Assessments** | | | | | | | | | | | | | | | | | | | |
| Review AEs | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Full Physical Examination | X | | | | | | | | | | | | | | | | | | |
| Directed Physical Examination | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | |
| Vital Signs and Weight[d] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | |
| ECOG Performance Status | X[e] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | |
| **Laboratory Procedures/Assessments: Analysis Performed by Local Laboratory** | | | | | | | | | | | | | | | | | | | |
| Pregnancy Test - Serum β-hCG[f] | X | | | | | | | | | | | | | | | | | | |
| PT/INR and aPTT[g] | X[h] | | | | | | | | | | | | | | | | | | |
| CBC with Differential[i,j] | X[h] | X | X | X | X | X | X | X | X | X | X | | X[i] | X | X | X | X | | |
| Comprehensive Chemistry | X[h] | X | X | X | X | X | X | X | X | X | X | | X[i] | X | X | X | X | | |

| Activity | Second Course Treatment Cycles[a] | | | | | | | | | | | | | End of Second Course Treatment | | Follow-up | | | Survival Follow-up |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | | | | | | 1 | 2 | Every 3 Months after Visit 2 | Every 12 weeks or as directed by the Sponsor[b] |
| **Treatment Cycle/ Scheduled Time** | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 and beyond | Discontinuation Visit | Safety Follow-up Visit | Follow-up Visit 1 | Follow-up Visit 2 | Follow-up Visit 3 and Beyond | Survival Follow-up Visit 1 and Beyond |
| **Scheduling Window (Days):** | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | ±3 | At study drug discontinuation ±3 | 30 days from last dose ±3 | ±7 days | ±7 days | ±7 days | ±14 days |
| Panel[i,j] | | | | | | | | | | | | | | | | | | | |
| Urinalysis[j,k] | X[h] | | | | X | | | | X | | | | X[k] | X | X | | | | |
| TSH, FT3/T3, FT4/T4[j,l] | X[h] | | X | | X | | X | | X | | X | | X[m] | X | X | | | | |
| ACTH[j] | X[h] | | | | | | | | | | | | X[m] | | | | | | |
| **Efficacy Measurements** | | | | | | | | | | | | | | | | | | | |
| Tumor Imaging | X | | | X | | | X | | | X | | | X | X | X | X | X | X | |

[a] In general, assessments/procedures are to be performed on Day 1 and prior to the first dose of trial treatment for each cycle unless otherwise specified. Treatment cycles are 3 weeks (21 days). If treatment cycles are adjusted, all procedures except imaging will be completed according to the cycle number and not weeks on treatment; imaging will be performed every 12 weeks (84 ± 7 days) from the date of first dose of second course.

[b] After documented local site-assessed disease progression, or the start of new anticancer treatment; contacts are approximately every 12 weeks by telephone. Updated survival status may be requested by the Sponsor at any time during the course of the study. Upon Sponsor notification, all subjects who do not/will not have a scheduled study visit or study contact during the Sponsor defined time period will be contacted for their survival status (excluding subjects that have a death event previously recorded).

[d] Vital signs to include temperature, pulse, respiratory rate, blood pressure, and weight.

[e] ECOG assessment for eligibility needs to be performed no more than 7 days prior first dose. If ECOG can't be performed within that time frame, second course Cycle 1, Day 1 ECOG may be utilized.

[f] For women of reproductive potential, a serum pregnancy test will be performed within 72 hours prior to the first second course dose. Serum pregnancy test should be repeated if required by local guidelines.

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

[h] Laboratory tests for determining eligibility for Second Course Phase are to be performed within 10 days prior to the first dose of pembrolizumab. See Section 7.1.3 – Laboratory Procedures/Assessments for details regarding laboratory tests.

[i] CBC with differentials and chemistry will be performed every cycle up to Cycle 11, then thereafter at Cycle 13, Cycle 15 etc.

[j] After the first dose, laboratory samples can be collected up to 7 days prior to the scheduled time point. Laboratory results must be known and acceptable prior to dosing, except endocrine testing which must be reviewed prior to the next dose of treatment. See Section 7.1.3 – Laboratory Procedures/Assessments for details regarding laboratory tests.

[k] Perform every 4 cycles.

[l] FT3/T3 and FT4/T4 are only required if TSH is out of the normal range.

[m] Perform TSH, FT3/T3, and FT4/T4 testing every other cycle from 13 onward (13, 15, 17, etc.), and ACTH as clinically indicated.

Abbreviations: ACTH=adrenocorticotropic hormone; AE=adverse event; aPTT/PTT=activated prothrombin time/partial thromboplastin time; β-hCG=beta-human chorionic gonadotropin; CBC=complete blood count; ECOG=Eastern Cooperative Oncology Group; EGFR=epidermal growth factor receptor; FT3=Free triiodothyronine; FT4=Free thyroxine; PT/INR=prothrombin time/International Normalized Ratio; TSH=thyroid stimulating hormone.

# 7.0 TRIAL PROCEDURES

## 7.1 Trial Procedures

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

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

### 7.1.1 Administrative Procedures

#### 7.1.1.1 Informed Consent

The investigator or qualified designee must obtain documented consent from each potential subject or each subject's legally acceptable representative prior to participating in a clinical trial or Future Biomedical Research. If there are changes to the subject's status during the trial (e.g., health or age of majority requirements), the investigator or qualified designee must ensure the appropriate consent is in place.

##### 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/IEC requirements, applicable laws and regulations and Sponsor requirements.

#### 7.1.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

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

### 7.1.1.2 Inclusion/Exclusion Criteria

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

### 7.1.1.3 Subject Identification Card

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

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

### 7.1.1.5 Prior and Concomitant Medications Review

#### 7.1.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the subject within 30 days before starting the trial. Treatment for the disease for which the subject has enrolled in this trial 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 Safety Follow-up Visit. In addition, new medications started during the Second Course Phase through the Second Course Safety Follow-up Visit should be recorded.

All medications related to reportable SAEs and ECIs should be recorded as defined in Section 7.2 – Assessing and Recording Adverse Events.

#### 7.1.1.6 Nonsmall Cell Lung Cancer Disease Details and Treatments

##### 7.1.1.6.1 Disease Details

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

##### 7.1.1.6.2 Prior Treatment

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

##### 7.1.1.6.3 Subsequent Antineoplastic Therapy Status

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

#### 7.1.1.7 Assignment of Screening Number

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

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

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

#### 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 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)

Interruptions from the protocol specified treatment plan for greater than 12 weeks due to pembrolizumab toxicity require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on subject management.

Study intervention(s) will be administered by the investigator and/or study staff according to the specifications within the Pharmacy Manual. The total volume of trial medication infused

will be compared with the total volume prepared to determine compliance with each dose administered.

### 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 AEs as specified in Section 6.0 – Trial Flow Chart and more frequently if clinically indicated. AEs 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.

Please refer to Section 7.2 – Assessing and Recording Adverse Events for detailed information regarding the assessment and recording of AEs.

#### 7.1.2.2 Physical Examination

##### 7.1.2.2.1 Full Physical Examination

The investigator or qualified designee will perform a complete physical examination during the screening period. Clinically significant abnormal findings should be recorded as medical history. The time points for full physical examination are described in Section 6.0 – 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 Examination

For cycles that do not require a full physical examination per the Section 6.0 – Trial Flow Chart, the investigator or qualified designee will perform a directed physical examination as clinically indicated prior to trial treatment administration. New clinically significant abnormal findings should be recorded as AEs.

#### 7.1.2.3 Vital Signs

Vital signs include temperature, pulse, respiratory rate, weight, and blood pressure. The investigator or qualified designee will take vital signs at screening, prior to the administration of each dose of trial treatment and during the Follow-up period as specified in Section 6 – Trial Flow Chart. Height will be measured at Visit 1 only.

#### 7.1.2.4 Lead Electrocardiogram

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. Further monitoring by ECG should be performed as clinically indicated.

#### 7.1.2.5 Eastern Cooperative Oncology Group Performance Status Scale

The investigator or qualified designee will assess ECOG Performance Status (see Section 12.3 – ECOG Performance Status) at screening, prior to the administration of each dose of study treatment and during the Follow-up Period as specified in Section 6 – Trial Flow Chart.

#### 7.1.2.6 Tumor Imaging and Assessments of Disease

The process for image collection and transmission to the central imaging vendor can be found in the Site Imaging Manual (SIM). All scheduled tumor imaging, including screening, must include complete imaging of the chest, abdomen, and pelvis. Tumor imaging is strongly preferred to be acquired by CT with iodinated contrast. For the abdomen and pelvis, magnetic resonance imaging (MRI) may be used when CT with iodinated contrast is contraindicated, or when local practice mandates it. Chest imaging must be done by CT, but may be done without contrast when iodinated contrast is contraindicated. Brain imaging should be provided when clinically indicated and at screening, as described below, for subjects with previously treated brain metastases. MRI is the strongly preferred modality for imaging the brain. The same imaging technique regarding modality, ideally the same scanner, and the use of contrast should be used in a subject throughout the study to optimize the reproducibility of the assessment of existing and new tumor burden and improve the accuracy of the assessment of response or progression based on imaging.

Subject eligibility will be determined using local assessment (investigator assessment) based on RECIST 1.1. All scheduled images for all study subjects from the sites will be submitted to the central imaging vendor. In addition, images (including via other modalities) that are obtained at an unscheduled time point to determine disease progression, as well as imaging obtained for other reasons, which show radiologic progression, should also be submitted to the central imaging vendor.

When the investigator identifies radiographic progression per RECIST 1.1, the central imaging vendor will perform expedited verification of radiologic PD and communicate the results to the trial site and Sponsor. If the investigator elects to implement iRECIST following initial investigator determination of PD, the investigator will assess for confirmation of progression by iRECIST at subsequent time points. Images should continue to be submitted to the central imaging vendor.

##### 7.1.2.6.1 Initial Tumor Imaging

Initial tumor imaging at screening must be performed within 30 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.

The screening images must be submitted to the central imaging vendor for retrospective review.

Tumor imaging performed as part of routine clinical management is acceptable for use as screening tumor imaging if they are of diagnostic quality and performed within 30 days prior to the date of randomization and can be assessed by the central imaging vendor.

Subjects with previously treated brain metastases may participate provided they are:

a) Radiologically stable, i.e., without evidence of progression (confirmed by MRI if MRI was used at prior imaging, or confirmed by CT imaging if CT was used at prior imaging) for at least 4 weeks by repeat imaging (note that the repeat imaging should be performed during study screening).

b) Clinically stable and without requirement of steroid treatment for at least 14 days prior to first dose of trial treatment. This exception does not include carcinomatous meningitis, as subjects with carcinomatous meningitis are excluded regardless of clinical stability.

Imaging used to confirm no evidence of progression of brain metastases must be submitted to the central imaging vendor for retrospective review as part of the screening assessment.

#### 7.1.2.6.2 Tumor Imaging During the Study

The first on-study imaging assessment should be performed at 9 weeks (63 days ±7 days) from the date of randomization. Subsequent tumor imaging should be performed every 9 weeks (63 days ±7 days) or more frequently if clinically indicated. After 54 weeks (378 days ±7 days), subjects who remain on treatment will have imaging performed every 12 weeks (84 days ±7 days). Imaging timing should follow calendar days and should not be adjusted for delays in cycle starts. Imaging should continue to be performed until disease progression is identified by the investigator and verified by the central imaging vendor (unless the investigator elects to continue treatment and follow iRECIST), the start of new anticancer treatment, withdrawal of consent, or death, whichever occurs first. All supplemental imaging must be submitted to the central imaging vendor.

PR and CR should be confirmed by a repeat imaging assessment. The imaging may be performed, at the earliest, 4 weeks after the first indication of a response, or at the next scheduled scan (i.e., 9 or 12 weeks later), whichever is clinically indicated. Subjects will then return to regular scheduled imaging every 9 or 12 weeks as described above, starting with the next scheduled imaging time point. Subjects who receive additional imaging for confirmation do not need to undergo the next scheduled tumor imaging if it is less than 4 weeks later; tumor imaging may resume at the subsequent scheduled imaging time point.

Per iRECIST (Section 7.1.2.6.6), disease progression should be confirmed by the site 4 to 8 weeks after central verification of site-assessed first radiologic evidence of PD in clinically stable subjects. Subjects who have unconfirmed disease progression may continue on treatment at the discretion of the investigator until progression is confirmed by the site provided they have met the conditions detailed in Section 7.1.2.6.6. Subjects who receive confirmatory imaging do not need to undergo the next scheduled tumor imaging if it is less than 4 weeks later; tumor imaging may resume at the subsequent scheduled imaging time point, if clinically stable. Subjects who have confirmed disease progression by iRECIST, as assessed by the site, will discontinue study treatment. Exceptions are detailed in Section 7.1.2.6.6.

#### 7.1.2.6.3 End of Treatment and Follow-up Tumor Imaging

In subjects who discontinue study treatment, tumor imaging should be performed at the time of treatment discontinuation (±4 week window). If previous imaging was obtained within 4 weeks prior to the date of discontinuation, then imaging at treatment discontinuation is not mandatory. In subjects who discontinue study treatment due to documented disease progression, and the investigator elects not to implement iRECIST, this is the final required tumor imaging.

In subjects who discontinue study treatment without documented disease progression, every effort should be made to continue monitoring their disease status by tumor imaging using the same imaging schedule used while on treatment (every 9 weeks in Year 1 or every 12 weeks after Year 1) to monitor disease status until the start of a new anticancer treatment, disease progression, death, withdrawal of consent, or the end of the study, whichever occurs first.

#### 7.1.2.6.4 Second Course (Retreatment) Tumor Imaging

**NOTE: As of Amendment 06, ipilimumab and matching placebo have been removed from the study. This section has been updated accordingly.**

Tumor imaging must be performed within 30 days prior to restarting treatment with pembrolizumab monotherapy. Before a subject may enter Second Course Phase, BICR verification of PD must have occurred. The PD imaging may also be used as the second course baseline imaging if it is within 30 days prior to restarting treatment and otherwise meets the baseline standards outlined in the SIM.

The first second course on study imaging assessment should be performed at 12 weeks (84 days ±7 days) after the restart of treatment. Subsequent tumor imaging should be performed every 12 weeks (84 days ±7 days) or more frequently if clinically indicated. Imaging for the Second Course Phase is not required to be transmitted to the central imaging vendor.

If during the second course tumor imaging shows initial PD per local RECIST 1.1, the investigator may elect to implement iRECIST and repeat the imaging 4 to 8 weeks later in order to confirm PD with the option of continuing treatment on second course while awaiting radiologic confirmation of progression. Subjects who obtain confirmatory imaging do not need to undergo scheduled tumor imaging if it is less than 4 weeks later and may wait until the next scheduled imaging time point, if clinically stable.

Imaging should continue to be performed until disease progression, the start of a new anticancer treatment, withdrawal of consent, death, or notification by the Sponsor, whichever occurs first.

In subjects who discontinue second course study treatment, tumor imaging should be performed at the time of treatment discontinuation. If previous imaging was obtained within 4 weeks prior to the date of discontinuation, then imaging at treatment discontinuation is not mandatory. In subjects who discontinue study treatment due to documented PD, this is the final required tumor imaging.

In subjects who discontinue second course study treatment without documented PD, every effort should be made to continue monitoring their disease status by radiologic imaging every

12 weeks (84 days ± 7 days) until the start of new anticancer treatment, disease progression, death, or the end of the study, whichever occurs first. For these subjects, the next imaging would occur at the Discontinuation Visit, and then 12 weeks later. If a previous scan was obtained within 4 weeks prior to the date of discontinuation, then a scan at treatment discontinuation is not mandatory. The timing of second course follow-up visits (Section 6.2) may be scheduled to coincide with the subject's follow-up imaging. Once imaging is complete (e.g., PD, new antineoplastic therapy), the subject enters into Survival Follow-up.

#### 7.1.2.6.5 RECIST 1.1 Assessment of Disease

RECIST 1.1 will be used by BICR as the primary measure for assessment of tumor response, date of disease progression, and as a basis for all protocol guidelines related to disease status (e.g., discontinuation of study treatment). Although RECIST 1.1 references a maximum of 5 target lesions in total and 2 per organ, the Sponsor allows a maximum of 10 target lesions in total and 5 per organ, if clinically relevant to enable a broader sampling of tumor burden.

#### 7.1.2.6.6 iRECIST Assessment of Disease

iRECIST is based on RECIST 1.1, but adapted to account for the unique tumor response seen with immunotherapeutic drugs. iRECIST will be used by the investigator to assess tumor response and progression, and make treatment decisions. When clinically stable, subjects should not be discontinued until progression is confirmed by the investigator, working with local radiology, according to the rules outlined in Section 12.4. This allowance to continue treatment despite initial radiologic PD takes into account the observation that some subjects can have a transient tumor flare in the first few months after the start of immunotherapy, and then experience subsequent disease response. This data will be captured in the clinical database.

Clinical stability is defined as the following:

- Absence of symptoms and signs indicating clinically significant progression of disease
- No decline in ECOG Performance Status
- No requirements for intensified management, including increased analgesia, radiation, or other palliative care

Any subject deemed **clinically unstable** should be discontinued from study treatment at site-assessed first radiologic evidence of PD, and is not required to have repeat tumor imaging for confirmation of PD by iRECIST.

If the investigator decides to continue treatment, the subject may continue to receive study treatment and the tumor assessment should be repeated 4 to 8 weeks later to confirm PD by iRECIST, per investigator assessment. Images should continue to be sent in to the central imaging vendor for potential retrospective BICR.

If repeat imaging does not confirm PD per iRECIST, as assessed by the investigator, and the subject continues to be clinically stable, study treatment may continue and follow the regular imaging schedule. If PD is confirmed, subjects will be discontinued from study treatment.

If a subject has confirmed radiographic progression (iCPD) as defined in Section 12.4, study treatment should be discontinued; however, if the subject is achieving a clinically meaningful benefit, an exception to continue study treatment may be considered following consultation with the Sponsor. In this case, if study treatment is continued, tumor imaging should continue to be performed following the intervals as outlined in the Trial Flow Chart in Section 6 and submitted to the central imaging vendor.

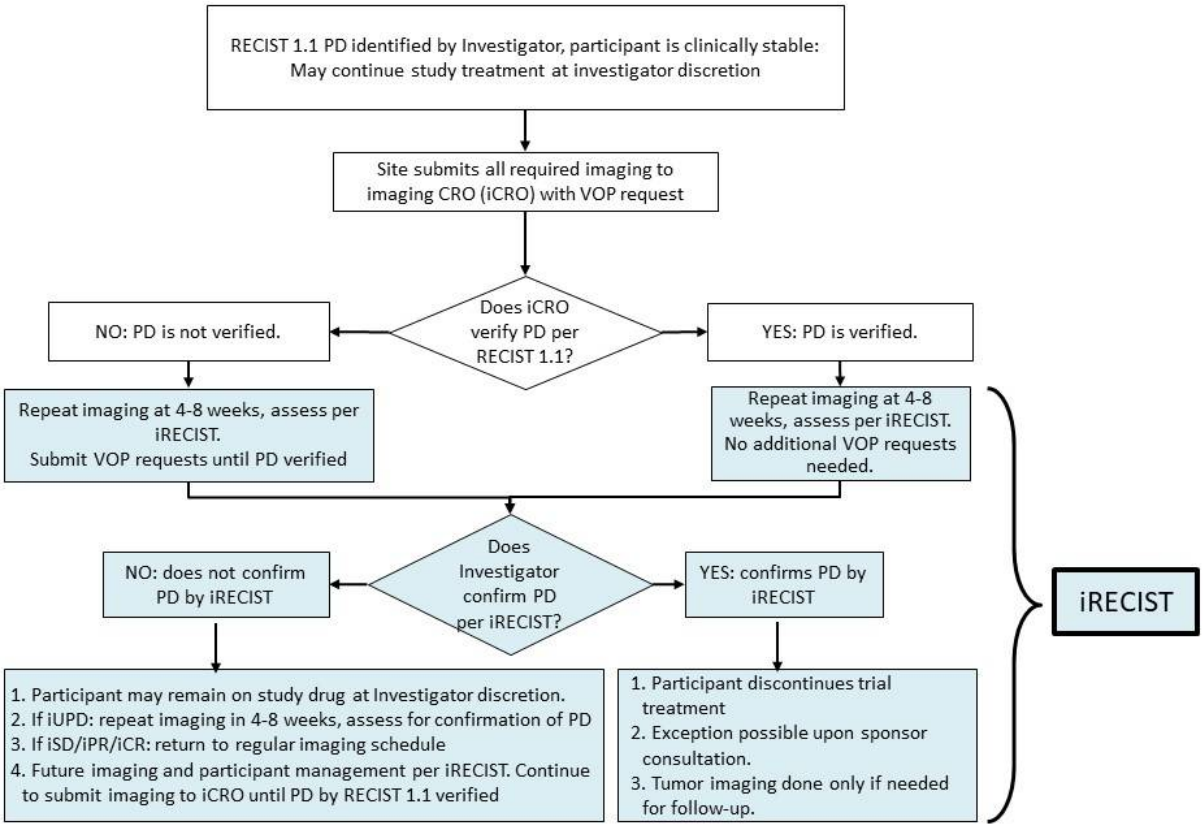
A description of the adaptations and iRECIST process is provided in Section 12.4, with additional details in the iRECIST publication [1]. A summary of imaging and treatment requirements after first radiologic evidence of progression is provided in Table 8 and illustrated as a flowchart in Figure 3.

Table 8 Imaging and Treatment After First Radiologic Evidence of Progressive Disease

| | Clinically Stable | | Clinically Unstable | |
|---|---|---|---|---|
| | **Imaging** | **Treatment** | **Imaging** | **Treatment** |
| First radiologic evidence of PD by RECIST 1.1 per investigator assessment. | Submit the imaging to BICR for verification. Repeat imaging at 4 to 8 weeks to confirm PD per iRECIST. | May continue study treatment at the discretion of the investigator. | Submit the imaging to BICR for verification. | Discontinue study treatment |
| Repeat tumor imaging confirms PD (iCPD) by iRECIST per investigator assessment | No additional imaging required. | Discontinue study treatment (exception is possible upon consultation with Sponsor). | No additional imaging required. | Not applicable |
| Repeat tumor imaging shows iUPD by iRECIST per investigator assessment | Repeat imaging at 4 to 8 weeks to confirm PD. | Continue study treatment at the investigator's discretion. | No additional imaging required. | Discontinue study treatment |
| Repeat tumor imaging shows iSD, iPR, or iCR by iRECIST per investigator assessment. | Continue regularly scheduled imaging assessments. | Continue study treatment at the investigator's discretion. | No additional imaging required. | Discontinue study treatment |

Abbreviations: BICR=blinded independent central review; iCPD=iRECIST confirmed progressive disease; iCR=iRECIST complete response; iRECIST=modified Response Evaluation Criteria in Solid Tumors 1.1 for immune-based therapeutics; iPR=iRECIST partial response; iSD=iRECIST stable disease; iUPD=iRECIST unconfirmed progressive disease; PD=progressive disease; RECIST 1.1=Response Evaluation Criteria in Solid Tumors 1.1.
Note: If progression has been centrally verified, further management is by the site, based on iRECIST. Any further imaging should still be submitted to the central imaging vendor, but no rapid review will occur. If RECIST 1.1 PD has not been centrally verified, ideally the site should continue treatment. Whether or not treatment continues, imaging should be collected and submitted to the central imaging vendor with verification of progression (VOP) request until RECIST 1.1 PD is verified by BICR.

Figure 3 Imaging and Treatment for Clinically Stable Subjects After First Radiologic Evidence of PD Assessed by the Investigator




### 7.1.2.7 Tumor Tissue Collection

Programmed death-ligand 1 expression will be tested by a central laboratory as part of screening. Only subjects whose tumors demonstrate PD-L1 expression (TPS ≥50%) are eligible for enrollment.

Archival tumor tissue sample or newly obtained core or excisional biopsy of a tumor lesion not previously irradiated must be provided to the central laboratory for testing. Formalin-fixed, paraffin-embedded tissue blocks are preferred to slides. Newly obtained biopsies are preferred to archived tissue.

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

Detailed instructions for tissue collection, processing and shipment are provided in the Procedures Manual. Older biopsy material or surgical specimens may be used to assess *EGFR* mutation.

#### 7.1.2.8 Patient-reported Outcomes

**NOTE: As of Amendment 06, PROs will no longer be collected. This section is no longer applicable and has been deleted.**

### 7.1.3 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below. The total amount of blood/tissue to be drawn/collected over the course of the trial (from pre-trial to post-trial visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per subject can be found in the Trial Procedures Manual. Refer to Section 6 − Trial Flow Chart for the timing of laboratory assessments.

#### 7.1.3.1 Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

**NOTE: As of Amendment 06, ipilimumab and matching placebo have been removed from the study. This section has been updated accordingly.**

Laboratory tests for hematology, chemistry and urinalysis are specified in Table 9. These tests are required at visits as noted in the Trial Flow Charts (Section 6) or as clinically indicated.

Table 9 Laboratory Tests

| Hematology | Chemistry | Urinalysis | Other |
|---|---|---|---|
| Hematocrit | Albumin | Blood | FSH |
| Hemoglobin | Alkaline phosphatase | Glucose | Serum β-hCG |
| Platelet count | ALT | Protein | Triiodothyronine (FT3 or T3) |
| WBC (total and/or differential) RBC | AST | Specific gravity | Thyroxine (FT4 or T4) |
| | Carbon dioxide ($CO_2$ or bicarbonate)[a] | Microscopic examination, if abnormal results are noted | TSH |
| | Calcium | | ACTH level[c] |
| | Chloride | | PT (INR) |
| | Creatinine | | aPTT/PTT |
| | Glucose | | |
| | Magnesium | | |
| | Phosphorus | | Blood for FBR (optional) |
| | Potassium | | Blood for genetics |
| | Sodium | | Blood for correlative studies |
| | Total bilirubin | | Blood for biomarkers |
| | Direct bilirubin, if total bilirubin is elevated above the ULN | | |

| Hematology | Chemistry | Urinalysis | Other |
|---|---|---|---|
| | Total protein | | |
| | BUN[b] | | |
| | Urea[b] | | |
| | Uric acid | | |

[a] If these tests are not done as part of standard of care in your region, then these tests do not need to be performed.
[b] BUN or urea should be collected per institutional standard. It is not required to perform both of these laboratory tests.
[c] Perform ACTH testing as clinically indicated.
Abbreviations: ACTH = adrenocorticotropic hormone; ALT = Alanine aminotransferase; AST = aspartate aminotransferase; BUN=Blood urea nitrogen; β-hCG=beta-human chorionic gonadotropin; CBC=complete blood count; $CO_2$=Carbon dioxide; FBR = future biomedical research; FSH=Follicle stimulating hormone; PPT/INR=Prothrombin time/international normalized ratio; aPTT/PTT=Activated prothrombin time/partial thromboplastin time; TSH = thyroid stimulating hormone; WBC=white blood cell.

Laboratory tests for screening or entry into the Second Course Phase should be performed within 10 days prior to the first dose of trial treatment. After Cycle 1, predose laboratory procedures can be conducted up to 7 days prior to dosing.

All protocol-required screening and safety laboratory results must be reviewed by the investigator or qualified designee and found to be acceptable prior to each dose of trial treatment.

Note: For endocrine testing (TSH, FT3/T3, FT4/T4, and ACTH as listed above), where results are not available prior to the dose of trial treatment, testing must be reviewed by the investigator or qualified designee and found to be acceptable prior to the following dose of trial treatment (eg, within 3 weeks of the laboratory procedure date).

#### 7.1.3.2 Pregnancy Test

For all women who are being considered for participation in the trial, and who are of reproductive potential, a serum pregnancy test after screening should be repeated if required by local guidelines. Subjects must be excluded/discontinued from the trial in the event of a positive or borderline-positive test result.

#### 7.1.3.3 Pharmacokinetic/Pharmacodynamic/Immunogenicity Evaluations

**NOTE: As of Amendment 06, pharmacokinetic, pharmacodynamic, and immunogenicity evaluations will not be pursued and blood samples for these endpoints will not be collected. This section is no longer applicable and has been deleted.**

#### 7.1.3.4 Molecular Testing

Site must be able to provide documentation of subject's tumor *EGFR* mutation and/or ALK translocation status. Investigators must be able to produce the source documentation of the *EGFR* mutation and *ALK* translocation in all subjects with nonsquamous histologies AND for subjects in whom testing is clinically recommended. If either an *EGFR*-sensitizing mutation or ALK translocation is detected, additional information regarding the mutation status of the other molecule is not required. If documentation is unavailable or the site is unable to test for these molecular changes, formalin-fixed paraffin-embedded tumor tissue of any age should be submitted to a local laboratory designated by the Sponsor for such testing. If the site is unable to provide this source documentation, then the Sponsor will offer this molecular

testing of the tumor. Tissue PD-L1 testing is assessed by IHC as determined by an FDA-approved test (22C3 Pharm IHC PharmDx [Dako]) assay) at a central laboratory. Local testing of PD-L1 is NOT allowed per protocol. Detailed instructions for tissue collection, processing, and shipment are provided in the Procedures Manual.

If treatment with ROS1-targeted therapy and testing for *ROS1* are approved and accessible, then local testing for *ROS1* is required. Testing for ROS1 is not required in subjects whose tumor is known to have predominantly squamous histology, and in subjects where *ROS1*-targeted therapy is not accessible.

#### 7.1.3.5 Planned Genetic Analysis Sample Collection

Sample collection, storage and shipment instructions for Planned Genetic Analysis samples will be provided in the Procedure Manual. Samples should be collected for planned analysis of associations between genetic variants in germline/tumor DNA and drug response. If a documented law or regulation prohibits (or local IRB/Independent Ethics Committee [IEC] does not approve) sample collection for these purposes, then such samples should not be collected at the corresponding sites. Leftover DNA extracted from planned genetic analysis samples will be stored for future biomedical research only if subject signs the Future Biomedical Research consent.

#### 7.1.3.6 Future Biomedical Research Samples

The following specimens are to be obtained as part of Future Biomedical Research:

- DNA for future research
- Leftover main study tumor tissue
- Leftover RNA from RNA analyses
- Leftover plasma from plasma biomarker analyses
- Leftover serum from serum biomarker analyses

#### 7.1.3.7 Medical Resource Utilization and Health Economics

All-cause hospitalizations and emergency room visits must be reported in the eCRF, from the time of treatment allocation/randomization through 90 days following cessation of study treatment, or 30 days following cessation of study treatment if the participant initiates new anticancer therapy (whichever is earlier).

### 7.1.4 Other Procedures

#### 7.1.4.1 Withdrawal/Discontinuation

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

#### 7.1.4.1.1 Withdrawal From Future Biomedical Research

Subjects may withdraw their consent for Future Biomedical Research. Subjects may withdraw consent at any time by contacting the principal investigator for the main trial. If medical records for the main trial are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@merck.com). Subsequently, the subject's consent for Future Biomedical Research will be withdrawn. A letter will be sent from the Sponsor to the investigator confirming the withdrawal. It is the responsibility of the investigator to inform the subject of completion of withdrawal. Any analyses in progress at the time of request for withdrawal or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research trial data and results. No new analyses would be generated after the request is received.

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

### 7.1.4.2 Subject Blinding/Unblinding

**NOTE: As of Amendment 06, blinding is no longer applicable as ipilimumab and matching placebo have been removed from the study. Subjects who remain on treatment will receive open-label pembrolizumab monotherapy as per protocol. Text related to ipilimumab/matching placebo and emergency unblinding in this section is no longer applicable.**

STUDY TREATMENT IDENTIFICATION INFORMATION IS TO BE UNMASKED ONLY IF NECESSARY FOR THE WELFARE OF THE PARTICIPANT. EVERY EFFORT SHOULD BE MADE NOT TO UNBLIND THE PARTICIPANT UNLESS NECESSARY.

For emergency situations where the investigator or delegate needs to identify the drug used by a subject and the dosage administered in case of emergency e.g., the occurrence of serious adverse events, he/she will contact the emergency unblinding call center by telephone and make a request for emergency unblinding. As requested by the investigator or delegate the emergency unblinding call center will provide the information to him/her promptly and report unblinding to the Sponsor. Prior to contacting the emergency unblinding call center to request unblinding of a subject's treatment assignment, the investigator or delegate must enter the toxicity grade of the adverse events observed, the relation to study drug, the reason thereof, etc., in the medical chart etc.

For studies that require non-emergency unblinding as part of the study design (eg, disease progression) to support treatment decisions, instructions in this section below should be followed. The emergency unblinding center should not be used for this purpose.

Subjects whose treatment assignment has been unblinded by the investigator/delegate and/or non-study treating physician must be discontinued from study drug, but should continue to be monitored in the trial.

For studies that require unblinding as part of the study design (e.g., disease recurrence, progression, or completion of study treatment) to support treatment decisions, the site must first contact the Sponsor for approval of nonemergent unblinding at the time of central laboratory confirmation of disease recurrence, disease progression, or completion of study treatment. Once authorization is granted by the Sponsor for nonemergent unblinding, the site will contact IVRS/IVXS to receive the participant's unblinded treatment arm. The emergency unblinding center should not be used for nonemergency unblinding.

Treatment/Vaccine identification information is to be unmasked ONLY if necessary for the welfare of the subject. Every effort should be made not to unblind the subject unless necessary.

In the event that unblinding has occurred, the circumstances around the unblinding (e.g., date, reason and person performing the unblinding) must be documented promptly, and the Sponsor Clinical Director notified as soon as possible. Only the principal investigator or delegate and the respective subject's code should be unblinded. Other trial site personnel and Sponsor personnel directly associated with the conduct of the trial should not be unblinded.

#### 7.1.4.3 Calibration of Equipment

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

### 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

Within 30 days prior to treatment randomization, potential subjects will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5.1. Visit requirements are outlined in the Trial Flow Chart (Section 6). Screening procedures may be repeated.

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 30 days prior to the first dose of trial treatment except for the following:

Laboratory tests are to be performed within 10 days prior to the first dose of trial treatment.

- ECOG performance must be assessed within 7 days of the first dose of trial treatment but before randomization.
- For women of reproductive potential, a serum pregnancy test will be performed within 72 hours prior to first dose of trial treatment.

- Tumor imaging must be performed within 30 days prior to the date of randomization.

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

#### 7.1.5.2 Treatment Period Visit

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

#### 7.1.5.3 End of Treatment Visits

##### 7.1.5.3.1 Discontinuation Visit

The Discontinuation Visit should occur at the time study drug is discontinued for any reason. If the Discontinuation Visit occurs 30 days from the last dose of study treatment, at the time of the mandatory Safety Follow-up Visit, procedures do not need to be repeated. Procedures at the time of discontinuation are detailed in Section 6.0 - Trial Flow Chart.

All subjects who discontinue trial treatment for a reason other than disease progression should continue to receive all assessments until PD by RECIST 1.1 or initiation of a new antineoplastic therapy.

Imaging assessments should continue as per the interval stated in the protocol; every 9 weeks for the first 54 weeks and then every 12 weeks thereafter. Additional imaging at the Discontinuation Visit is not required provided that a scan was obtained within 4 weeks prior to the date of discontinuation. In subjects who discontinue trial treatment due to documented disease progression, the scan documenting disease progression is the final required tumor imaging.

##### 7.1.5.3.2 Safety Follow-up Visit

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

Subjects who are eligible for retreatment during the Second Course Phase may have up to 2 Safety Follow-up Visits, the first after the Treatment Phase and the second after the Second Course Phase per the requirements in Section 7.1.5.5 – Second Course Phase.

Imaging assessments should continue as per the interval stated in the protocol; every 9 weeks for the first 54 weeks and then every 12 weeks thereafter. Additional imaging at the Safety Follow-up Visit is not required provided that imaging assessments have been performed per schedule.

#### 7.1.5.4 Follow-up Phase

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

##### 7.1.5.4.1 Follow-up Visits

All subjects who discontinue initial trial treatment or Second Course Phase trial treatment for a reason other than disease progression should continue to receive all assessments until PD by RECIST 1.1 or initiation of a new antineoplastic therapy.

Subjects who have received the maximum administrations of pembrolizumab indicated above for either initial treatment or Second Course Phase trial treatment, should be followed as indicated in the Follow-up Phase of the study outlined in Section 6.0 - Trial Flow Chart.

Follow-up Visit 1 should be scheduled to coincide with the next scheduled imaging visit to occur at least 9 weeks after the last dose of trial treatment. Assessment for drug-related AEs, including those consistent with immune phenomena, should occur at Follow-up Visit 1. Follow-up Visit 2 should be scheduled to coincide with the next scheduled imaging visit to occur at least 18 weeks after the last dose of trial treatment. After Follow-up Visit 2, subjects only need to be assessed every 9 weeks (63 ± 7 days) or 12 weeks (84 ± 7 days) as defined in Section 7.1.2.6 – Tumor Imaging and Assessments of Disease, by radiologic imaging to monitor disease status, development of drug-related SAEs and ECIs, and initiation of new antineoplastic therapy. Unless otherwise noted in Section 6.0 - Trial Flow Chart, every effort should be made to collect subject information on the start of new antineoplastic therapy, disease progression, and/or death.

Subjects who are eligible to receive retreatment according to the criteria in Section 7.1.5.6 – Second Course Phase will move to the Second Course Phase when they experience disease progression.

##### 7.1.5.4.2 Survival Follow-up

Once the subject stops the imaging assessments for this protocol (e.g., for PD or starting a new antineoplastic therapy), the subject moves into the Survival Follow-up Phase and should be contacted by telephone every 12 weeks (84 ± 14 days) to assess for survival status. Survival assessments and its respective entry into the database may be required more frequently around the projected interim or final analyses. Post-study treatments and the subject's response to them will also be collected at the same time.

Survival status data may be requested more frequently than every 12 weeks (84 ± 14 days) at specific time points during the study. For example, survival status may be requested prior to an external DMC safety review, efficacy IA, and FA. All subjects who are in the Survival Follow-up Phase, and not known to have died prior to the request for this additional survival status time points, will be contacted at that time.

Subjects may withdraw their consent at any time from any or all portions of the study. Subjects who withdraw consent for treatment and/or imaging are encouraged to remain on the noninvasive Survival Follow-up portion of the study. The only procedures associated with this phase are telephone contacts to assess survival status and the current state of the

subject's NSCLC. The noninvasive nature and societal benefit of Survival Follow-up should be explained to the subject by the site staff, particularly when discontinuing treatment and imaging.

#### 7.1.5.5 Survival Status

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

#### 7.1.5.6 Second Course Phase

**NOTE: As of Amendment 06, ipilimumab and matching placebo have been removed from the study. This section has been updated accordingly.**

Visit requirements are outlined in Section 6.0 – Trial Flow Chart. Specific procedure-related details are provided above in Section 7.1 – Trial Procedures. Subjects may be eligible to receive up to 17 additional trial treatments of pembrolizumab in the Second Course Phase. After the Second Course Phase, subjects should be followed for progression and survival as indicated, with no option for further retreatment on study.

Subjects will be eligible to receive pembrolizumab at the discretion of the investigator in the Second Course Phase of this study if the subject meets the following conditions:

**Either**

- Stopped their initial treatment with pembrolizumab after attaining a confirmed CR according to RECIST 1.1, and
  - Was treated for at least 8 cycles with pembrolizumab
  - Received at least 2 treatments with pembrolizumab beyond the date when the initial CR was declared

**OR**

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

**And**

- Experienced radiographic disease progression verified by BICR based on RECIST 1.1 after stopping initial treatment, and:
- Did not receive any anticancer treatment since the last dose of pembrolizumab
- Not more than 2 years have elapsed since discontinuing their initial treatment with pembrolizumab

- The subject meets all of the safety parameters listed in the inclusion criteria and none of the safety parameters listed in the exclusion criteria, and
- The study is ongoing

Subjects will be retreated at the same dose they last received pembrolizumab.

Imaging will be performed every 12 weeks (84 ± 7 days) after the first dose of Second Course Phase trial treatment until disease progression, or start of new antineoplastic therapy. The timing of imaging should follow calendar days and should not be adjusted for delays in cycle starts or extension of cycle frequencies. The same imaging technique should be used in a subject throughout the trial. Continued imaging is not needed for subjects who start another anticancer treatment regimen. An objective response or disease progression that occurs during the Second Course Phase for a subject will not be counted as an event for the primary analysis of either endpoint in this trial.

#### 7.1.5.7 Discontinued Subjects Continuing to be Monitored in the Trial

Subjects who discontinue treatment will be followed up for efficacy and OS until consent withdrawal from trial, becoming lost to follow-up, death, or end of the study, whichever comes first.

Date of disease recurrence or metastatic progression, start and stop dates of subsequent anticancer treatments, and reasons for treatments should be recorded in the appropriate eCRF. For subjects who die during the follow up period, the date and cause of death should be recorded in the appropriate eCRF.

## 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 Electronic Data Capture (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

**NOTE: As of Amendment 06, ipilimumab and matching placebo have been removed from the study. Subjects who remain on treatment will receive open-label pembrolizumab monotherapy as per protocol. Text related to ipilimumab/matching placebo in this section is no longer applicable and has been removed.**

For purposes of this trial, an overdose will be defined as any dose exceeding the prescribed dose for pembrolizumab as any dose of 1000 mg or exceeding 5 times the protocol-prescribed dose. No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, pembrolizumab 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, 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 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 trial 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 10 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 trial treatment, or 30 days following cessation of trial treatment if the subject initiates new anticancer therapy, whichever is earlier, any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study (reference Section 7.2.3.3 for additional details), whether or not related to the Sponsor's product, must be reported within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

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

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

#### 7.2.3.2 Events of Clinical Interest

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

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

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

Events of clinical interest for this trial include:

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

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

#### 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. Any adverse event which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the adverse event case report forms/worksheets.

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

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

Table 10 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.<br>**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?<br>If yes, did the AE resolve or improve?<br>If yes, this is a positive dechallenge. If no, this is a negative dechallenge.<br>(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?<br>If yes, did the AE recur or worsen?<br>If yes, this is a positive rechallenge. If no, this is a negative rechallenge.<br>(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).<br>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.

### 7.2.6 Executive Oversight Committee

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

### 7.2.7 Data Monitoring Committee

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

The DMC will make recommendations to the EOC regarding steps to ensure both subject safety and the continued ethical integrity of the trial. Also, the DMC will review interim trial results, consider the overall risk and benefit to trial participants (see Section 8.7 - Interim Analyses) and recommend to the EOC if the trial should continue in accordance with the protocol.

Specific details regarding composition, responsibilities, and governance, including the roles and responsibilities of the various members and the Sponsor protocol team; meeting facilitation; the trial governance structure; and requirements for and proper documentation of DMC reports, minutes, and recommendations will be described in the DMC charter that is reviewed and approved by all the DMC members.

The DMC has responsibility for assessment of the overall risk:benefit. Periodic safety monitoring will be specified in the DMC Charter with input from the DMC members. When prompted by safety concerns, the DMC can request corresponding efficacy data. Any DMC recommendation will be communicated to the Sponsor as agreed to in the DMC Charter. As of Amendment 06, no additional DMC reviews will take place.

## 8.0 STATISTICAL ANALYSIS PLAN

**NOTE: Data from the IA1 of KEYNOTE-598 (data cutoff: 01-SEP-2020) indicated that the study did not meet the prespecified success criteria for improvement in PFS or OS for the combination of pembrolizumab plus ipilimumab compared with pembrolizumab plus placebo. Furthermore, a nonbinding futility analysis was performed at IA1 at the request of the eDMC. This analysis showed the study met the criteria for declaring futility and the benefit-risk was not considered positive to continue the trial. Based upon these data and at the recommendation of the eDMC, no further prespecified analysis of primary and secondary endpoints will be performed. Exploratory objectives may not be pursued. Updates to the safety analyses are provided in Sec. 8.1 and Sec. 8.6.2.**

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, changes are made to primary and/or key secondary hypotheses or the statistical methods related to those hypotheses, but prior to any unblinding/final database lock, then the protocol will be amended (consistent with ICH Guideline E9). Changes to exploratory or other nonconfirmatory analyses made after the protocol has been finalized, but prior to unblinding/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. Separate analysis plans (i.e., separate documents from the sSAP) will be developed to detail PK analysis as well as biomarker analysis. The PRO analysis plan will be included in the sSAP.

## 8.1 Statistical Analysis Plan Summary

Key elements of the SAP are summarized in this section. The comprehensive plan is provided in Section 8.2 – Responsibility for Analyses/In-House Blinding through Section 8.12 – Extent of Exposure.

| | |
|---|---|
| **Study Design Overview** | Phase 3 study of Pembrolizumab + Ipilimumab versus Pembrolizumab + placebo in 1L, Stage IV, metastatic NSCLC subjects whose tumors express PD-L1 (TPS ≥ 50%). |
| **Treatment Assignment** | Subjects will be randomized in a 1:1 ratio between 2 treatment arms:<br>(1) pembrolizumab plus ipilimumab and (2) pembrolizumab plus placebo.<br>Stratification factors are as follows:<br>1) ECOG Performance Status (0 versus 1)<br>2) Geographic region (East Asia versus Non-East Asia)<br>3) Predominant tumor histology (squamous versus nonsquamous) |
| **Analysis Populations** | Efficacy: Intent-to-Treat (ITT)<br>Safety: All Subjects as Treated (ASaT) |
| **Primary Endpoints/ Hypotheses** | • OS<br>• PFS per RECIST 1.1 based on BICR |
| **Secondary Endpoints** | • ORR per RECIST 1.1 based on BICR<br>• DOR<br>• Safety and tolerability<br>• Change from baseline in global health status/quality of life score from the EORTC QLQ-C30 (items 29 and 30)<br>• TTD in PRO composite endpoint |
| **Statistical Methods for Key Efficacy Analyses** | The primary hypotheses will be evaluated by comparing pembrolizumab plus ipilimumab to pembrolizumab plus placebo in PFS and OS using a stratified log-rank test. The hazard ratio will be estimated using a stratified Cox regression model. Event rates over time will be estimated within each treatment group using the Kaplan-Meier method. The ORR will be evaluated using a stratified Miettinen and Nurminen method with strata weighting by sample size [40]. |
| **Statistical Methods for Key Safety Analyses** | **As of Amendment 06,** the safety analysis will include only the proportion of participants with certain AEs summarized by counts and percentages by treatment group. |

| | |
|---|---|
| **Interim Analyses** | **As of Amendment 06, IA1 is complete. The other prespecified analyses listed below will not be performed.**<br>Two efficacy IAs and one FA are planned in this study. Results will be reviewed by an external DMC. Details are provided in Section 8.7 – Interim Analyses.<br>• Interim analysis 1 (IA1): Approximately 255 deaths have been observed and ~ 12 months after the last subject randomized. The ORR p-value from IA1 may be evaluated for statistical significance if the PFS and/or OS null hypotheses are rejected at IA1 or a later time.<br>o Purpose: Interim PFS (~ 92% of target PFS events) and OS analyses (~ 71% of target OS events).<br>• Interim analysis 2 (IA2): Approximately 307 deaths have been observed and ~ 19 months after the last subject randomized.<br>o Purpose: Final PFS analysis and interim OS analysis (~ 85% of target OS events).<br>• Final analysis (FA): Approximately 361 deaths have been observed and ~ 27 months after the last subject randomized.<br>o Purpose: Final OS analysis. |
| **Multiplicity** | The overall Type I error rate over the multiple endpoints will be strongly controlled at 2.5% (one-sided). A 0.6% (one-sided) Type I error rate will be allocated to test PFS and 1.9% (one-sided) allocated to test OS. The graphical method of Maurer and Bretz [41] will be applied to reallocate alpha between the hypotheses of ORR, PFS and OS. Group sequential methods will be used to allocate alpha between the interim and final analyses for the PFS and OS endpoints. |
| **Sample Size and Power** | The planned sample size is approximately 568 subjects. With 389 PFS events, the study has ~ 87% power for detecting a hazard ratio of 0.69 at 0.6% (one-sided) significance level. With 361 deaths, the study has ~ 90% power for detecting a hazard ratio of 0.7 at 1.90 % (one-sided) significance level. |

## 8.2 Responsibility for Analyses/In-House Blinding

**Note: As of Amendment 06, the study will be unblinded to the Sponsor, the investigational sites, and the participants.**

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

This study will be conducted as a double-blinded study under in-house blinding procedures. The official, final database will not be unblinded until medical/scientific review has been performed, protocol deviations have been identified, and data have been declared final and complete.

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

Planned interim analyses are described in Section 8.7 – Interim Analyses. Blinding to treatment assignment will be maintained at all investigational sites. Treatment-level results of the planned interim analyses will be provided by the external unblinded statistician to the DMC. Limited additional Sponsor personnel may be unblinded to the treatment level results of the interim analyses, if required, in order to act on the recommendations of the DMC (e.g., interaction with regulatory agencies). The extent to which individuals are unblinded with respect to results of interim analyses will be documented by the unblinded statistician.

The DMC will serve as the primary reviewer of the results of the interim analyses and will make recommendations for discontinuation of the study or modification to an EOC of the Sponsor. Depending on the recommendation of the DMC, the Sponsor may prepare a regulatory submission. If the DMC recommends modifications to the design of the protocol or discontinuation of the study, this EOC and limited additional Sponsor personnel may be unblinded to results at the treatment level in order to act on these recommendations. The DMC responsibilities, review schedules, and additional logistical details will be provided in the DMC Charter.

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

## 8.3 Hypotheses/Estimation

Objectives and hypotheses of the study are stated in Section 3 – Objective(s) & Hypothesis(es).

## 8.4 Analysis Endpoints

Efficacy and safety endpoints that will be evaluated for within- and/or between-treatment differences are listed below. Exploratory endpoints will be described in the sSAP.

### 8.4.1 Efficacy Endpoints

**Primary Endpoints**

**Overall Survival**

OS is defined as the time from randomization to death due to any cause. Subjects without documented death at the time of analysis will be censored at the date of last known contact.

**Progression-free Survival**

PFS is defined as the time from randomization to the first documented disease progression per RECIST 1.1 based on BICR or death due to any cause, whichever occurs first. See Section 8.6.1.2 – Progression-free Survival for the definition of censoring.

**Secondary Endpoints**

**Objective Response Rate**

ORR is defined as the proportion of subjects who have a CR or a PR. Responses are based on confirmed assessments by BICR per RECIST 1.1.

**Duration of Response**

For subjects who demonstrate CR or PR, DOR is defined as the time from first documented evidence of CR or PR until disease progression per RECIST 1.1 as assessed by BICR or death due to any cause, whichever occurs first.

**Change from baseline in global health status/quality of life**

This is defined as a change from baseline in the global health status/quality of life score from the EORTC QLQ-C30 (items 29 and 30).

**Time to true deterioration in cough, pain in chest, and shortness of breath**

TTD is defined as the time to the first onset of a 10-point or greater score deterioration from baseline in any one of the 3 symptoms, confirmed by a second adjacent 10-point or greater score deterioration from baseline. Cough is based on EORTC QLQ-LC13 question 1, pain in chest is based on EORTC QLQ-LC13 question 10, and shortness of breath is based on EORTC QLQ-C30 question 8.

### 8.4.2 Safety Endpoints

Safety measurements are described in Section 4.2.3.3 – Safety Endpoints and Section 7 – Trial Procedures. Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs, SAEs, fatal AEs, laboratory tests, and vital signs. Safety parameters to be analyzed include, but are not limited to, AEs, SAEs, fatal AEs, and laboratory changes.

## 8.5 Analysis Populations

### 8.5.1 Efficacy Analysis Populations

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

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

### 8.5.2 Safety Analysis Populations

The All Subjects as Treated (ASaT) population will be used for the analysis of safety data in this study. The ASaT population consists of all randomized subjects who received at least 1 dose of study treatment. Subjects will be included in the treatment group corresponding to the study treatment they actually received for the analysis of safety data using the ASaT population. For most subjects, this will be the treatment group to which they are randomized. Subjects who take incorrect study treatment for the entire treatment period will be included in the treatment group corresponding to the study treatment actually received. Any subject who receives the incorrect study medication for 1 cycle, but receives the correct treatment for all other cycles, will be analyzed according to the correct treatment group and a narrative will be provided for any events that occur during the cycle for which the subject is incorrectly dosed.

At least 1 laboratory or vital sign measurement obtained after at least 1 dose of study treatment is required for inclusion in the analysis of each specific parameter. To assess change from baseline, a baseline measurement is also required. Details on the approach to handling missing data for safety analyses are provided in Section 8.6 – Statistical Methods.

### 8.5.3 Patient-reported Outcomes Analysis Populations

The PRO analyses are based on the PRO full analysis set (FAS) population, defined as subjects who have at least 1 PRO assessment available and have received at least 1 dose of study medication.

## 8.6 Statistical Methods

### 8.6.1 Statistical Methods for Efficacy Analyses

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

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

The stratification factors used for randomization (see Section 5.4 – Stratification) will be applied to all stratified analyses, in particular, the stratified log-rank test, stratified Cox model, and stratified Miettinen and Nurminen method [42]. In the event that there are small strata, for the purpose of analysis, strata will be combined to ensure sufficient number of participants, responses and events in each stratum. Details regarding the pooling strategy will be prespecified in the sSAP prior to the database lock for the first analysis when each applicable endpoint will be analyzed, and decisions regarding the pooling will be based on a blinded review of response and event counts by stratum.

#### 8.6.1.1 Overall Survival

The nonparametric Kaplan-Meier method will be used to estimate the survival curve in each treatment group. The treatment difference in survival will be assessed by the stratified log-rank test. A stratified Cox proportional hazard model with Efron's method of tie handling will be used to assess the magnitude of the treatment difference (i.e., the hazard ratio). The hazard ratio and its 95% CI from the stratified Cox model with Efron's method of tie handling and with a single covariate for treatment will be reported. The stratification factors used for randomization (see Section 5.4– Stratification) will be applied to both the stratified log-rank test and the stratified Cox model.

In case the proportional hazards assumption does not hold, Restricted Mean Survival Time (RMST) method may be conducted for OS to account for the possible nonproportional hazards effect as a sensitivity analysis.

#### 8.6.1.2 Progression-free Survival

The nonparametric Kaplan-Meier method will be used to estimate the PFS curve in each treatment group. The treatment difference in PFS will be assessed by the stratified log-rank test. A stratified Cox proportional hazard model with Efron's method of tie handling will be used to assess the magnitude of the treatment difference (i.e., hazard ratio) between the treatment groups. The hazard ratio and its 95% CI from the stratified Cox model with Efron's method of tie handling and with a single covariate for treatment will be reported. The stratification factors used for randomization (see Section 5.4 – Stratification) will be applied to both the stratified log-rank test and the stratified Cox model.

Since disease progression is assessed periodically, PD can occur any time in the time interval between the last assessment where PD was not documented and the assessment when PD is documented. For the primary analysis, for the subjects who have PD, the true date of disease

progression will be approximated by the date of the first assessment at which PD is objectively documented per RECIST 1.1 by BICR, regardless of discontinuation of study drug. Death is considered as a confirmed PD event.

In order to evaluate the robustness of the PFS endpoint per RECIST 1.1 by BICR, 2sensitivity analyses with a different set of censoring rules will be performed. The first sensitivity analysis is the same as the primary analysis except that the data for any subject who misses more than 1 disease assessment (with or without a subsequent death or progression) are censored at the last disease assessment prior to missing visits. The second sensitivity analysis is the same as the primary analysis except that it considers discontinuation of treatment or initiation of an anticancer treatment subsequent to discontinuation of study-specified treatments, whichever occurs later, to be a PD event for subjects without documented PD or death. If a subject meets multiple criteria for censoring, the censoring criterion that occurs earliest will be applied. The censoring rules for primary and sensitivity analyses are summarized in Table 11. In case there is an imbalance between the treatment groups on disease assessment schedules or censoring patterns, we will perform an additional PFS sensitivity analysis using time from randomization to scheduled tumor assessment time as opposed to actual tumor assessment.

In case the proportional hazards assumption is not valid, RMST method may be conducted for PFS to account for the possible nonproportional hazards effect as a sensitivity analysis.

Table 11 Censoring Rules for Primary and Sensitivity Analyses of PFS

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

| Situation | Primary Analysis | Sensitivity Analysis 1 | Sensitivity Analysis 2 |
|---|---|---|---|
| No PD and no death; new anticancer treatment is initiated | Censored at last disease assessment before new anticancer treatment | Censored at last disease assessment | Progressed at date of new anticancer treatment. |

Abbreviations: PFS=progression-free survival; PD=progressive disease.

#### 8.6.1.3 Objective Response Rate

The stratified Miettinen and Nurminen method will be used for comparison of the ORR between the 2 treatment groups. The difference in ORR and its 95% CI from the stratified Miettinen and Nurminen method with strata weighting by sample size will be reported. The stratification factors used for randomization (see Section 5.4– Stratification) will be applied to the analysis. Subjects without assessments are considered nonresponders.

#### 8.6.1.4 Duration of Response

For subjects who demonstrate CR or PR, DOR is defined as the time from first documented evidence of CR or PR until disease progression or death due to any cause, whichever occurs first. Censoring rules for DOR are summarized in Table 12.

For DOR analysis, a summary of the reasons responding subjects are censored will also be provided. Responding subjects who are alive, have not progressed, have not initiated new anticancer treatment, have not been determined to be lost to follow-up, and have had a disease assessment within ~ 5 months of the data cutoff date are considered ongoing responders at the time of analysis. If a subject meets multiple criteria for censoring, the censoring criterion that occurs earliest will be applied.

Table 12 Censoring Rules for Duration of Response

| Situation | Date of Progression or Censoring | Outcome |
|---|---|---|
| No progression nor death, no new anticancer therapy initiated | Last adequate disease assessment | Censor (nonevent) |
| No progression nor death, new anticancer therapy initiated | Last adequate disease assessment before new anticancer therapy initiated | Censor (nonevent) |
| Death or progression immediately after ≥ 2 consecutive missed disease assessments or after new anticancer therapy, if any | Earlier date of last adequate disease assessment prior to ≥ 2 missed adequate disease assessments and new anticancer therapy, if any | Censor (nonevent) |
| Death or progression after ≤ 1 missed disease assessments and before new anticancer therapy, if any | PD or death | End of response (Event) |
| Abbreviations: PD = progressive disease<br>A missed disease assessment includes any assessment that is not obtained or is considered inadequate for evaluation of response. | | |

If sample size permits, DOR will be summarized descriptively using the Kaplan-Meier method. Only the subset of subjects who show a CR or PR will be included in this analysis.

#### 8.6.1.5 Change from Baseline in Global Health Status/Quality of Life

The time point for the mean change from baseline will be determined based on blinded data review prior to the database lock for any PRO analysis and documented in the sSAP.

To assess the treatment effects on the PRO score change from baseline in the global health status/quality of life, a constrained longitudinal data analysis (cLDA) model proposed by Liang and Zeger [43] will be applied, with the PRO score as the response variable, and treatment, time, the treatment by time interaction, and stratification factors used for randomization (see Section 5.4 – Stratification) as covariates. The treatment difference in terms of least square (LS) mean change from baseline will be estimated from this model together with 95% CI. Model-based LS mean with 95% CI will be provided by treatment group for PRO scores at baseline and post-baseline time point.

#### 8.6.1.6 Time to True Deterioration in Cough, Pain in Chest, and Shortness of Breath

TTD is defined as the time to first onset of 10 or more deterioration from baseline with confirmation under right-censoring rule. Subjects with no confirmed deterioration from baseline will be censored at the date of their last observation. The nonparametric Kaplan-Meier method will be used to estimate the deterioration curve in each treatment group. The treatment difference in time to deterioration will be assessed by the stratified log-rank test. A stratified Cox proportional hazard model with Efron's method of tie handling will be used to assess the magnitude of the treatment difference (hazard ratio) between the treatment groups. The traditional time to deterioration, defined as the time to first onset of 10 or more deterioration from baseline without confirmation under right-censoring rule, may also be summarized.

#### 8.6.1.7 Analysis Strategies for Key Efficacy Endpoints

Table 13 summarizes the primary analysis approach for primary and secondary efficacy endpoints. Sensitivity analysis methods are described above for each endpoint as applicable.

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

Table 13 Analysis Strategy for Key Efficacy Endpoints

| Endpoint/Variable | Statistical Method[a] | Analysis Population | Missing Data Approach |
|---|---|---|---|
| **Primary:** | | | |
| OS | Test: Stratified log-rank test to assess the treatment difference<br>Estimation: Stratified Cox model with Efron's tie handling method to assess the magnitude of treatment difference | ITT | • Censored at last known alive date. |
| PFS per RECIST 1.1 by BICR | Test: Stratified log-rank test to assess the treatment difference<br>Estimation: Stratified Cox model with Efron's tie handling method to assess the magnitude of treatment difference | ITT | • Primary censoring rule<br>• Sensitivity analysis 1<br>• Sensitivity analysis 2<br>(More details are in Table 11). |
| **Secondary :** | | | |
| ORR per RECIST 1.1 by BICR | Stratified Miettinen and Nurminen method with sample size weights | ITT | Subjects without assessments are considered nonresponders. |
| DOR per RECIST 1.1 by BICR | Summary statistics using Kaplan-Meier method | All responders in ITT | Censoring rules in Table 12. |
| Change from baseline in global health status/quality of life (items 29 and 30) | cLDA model | PRO FAS | Missing at random |
| TTD | Test: Stratified log-rank test to assess the treatment difference<br>Estimation: Stratified Cox model with Efron's tie handling method to assess the magnitude of treatment difference | PRO FAS | Censoring at the last available assessment. |

[a] Statistical models are described in further detail in the text. For stratified analyses, the stratification factors used for randomization (Section 5.4 – Stratification) will be applied to the analysis.

Abbreviations: cLDA=constrained longitudinal data analysis; DOR=duration of response; PRO FAS=patient reported outcome full analysis set; ITT=intent-to-treat; ORR=objective response rate; OS=overall survival; RECIST=Response Evaluation Criteria in Solid Tumors Version 1.1; TTD=time to true deterioration.

### 8.6.2 Statistical Methods for Safety Analyses

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

**As of Amendment 06, the following safety analyses will be performed:** individual events and the broad AE categories including the proportion of participants with any AE, a drug-related AE, a serious AE, an AE which is both drug-related and serious, a Grade 3-5 AE, a drug-related Grade 3-5 AE, a fatal AE, dose interruption due to an AE, and discontinuation due to an AE will be summarized by counts and percentages by treatment group.

**As of Amendment 06, all other safety analyses listed in this section below will not be performed.**

The analysis of safety results will follow a tiered approach (Table 14). The tiers differ with respect to the analyses that will be performed. Adverse experiences (specific terms as well as system organ class terms) and events that meet predefined limits of change in laboratory and vital signs, and ECG parameters are either prespecified as Tier-1 endpoints or will be classified as belonging to "Tier 2" or "Tier 3," based on observed proportions of participants with an event.

**Tier 1 Events**

Safety parameters or AEOSI that are identified a priori constitute "Tier 1" safety endpoints that will be participant to inferential testing for statistical significance with p-values and 95% CIs provided for between-group comparisons. AEOSI that are immune-mediated or potentially immune-mediated are well documented and will be evaluated separately; however, these events have been characterized consistently throughout the pembrolizumab clinical development program and determination of statistical significance is not expected to add value to the safety evaluation. Based on toxicity data across the pembrolizumab program, the combination of pembrolizumab with ipilimumab is not anticipated to produce toxicity beyond what is expected for these therapies alone. Thus, there are no AEs that warrant elevation to Tier 1 in this study.

**Tier 2 Events**

Tier 2 parameters will be assessed via point estimates with 95% CIs provided for differences in the proportion of participants with events using the Miettinen and Nurminen method, an unconditional, asymptotic method [40].

Membership in Tier 2 requires that at least 10% of participants in any treatment group exhibit the event. The threshold of at least 10% of participants was chosen for Tier 2 event because the population enrolled in this study are in critical condition and usually experience various AEs of similar types regardless of treatment; events reported less frequent than 10% of participants would obscure the assessment of overall safety profile and add little to the interpretation of potentially meaningful treatment differences. In addition, Grade 3 to 5 AE (≥5% of participants in 1 of the treatment groups) and SAE (≥2% of participants in 1 of the treatment groups) will be considered Tier 2 endpoints. Because many 95% CIs may be

provided without adjustment for multiplicity, the CIs should be regarded as a helpful descriptive measure to be used in safety review, not a formal method for assessing the statistical significance of the between-group differences.

**Tier 3 Events**

Safety endpoints that are not Tier 1 or 2 events are considered Tier 3 events. Only point estimates by treatment group are provided for Tier 3 safety parameters (Table 14).

**Continuous Safety Measures**

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

Table 14 Analysis Strategy for Safety Parameters

| Safety Tier | Safety Endpoint | 95% CI for Treatment Comparison | Descriptive Statistics |
|---|---|---|---|
| Tier 2 | Specific AEs (incidence ≥10% of participants in one of the treatment groups) | X | X |
| | Specific Grade 3-5 AEs (incidence ≥5% of participants in one of the treatment groups) | X | X |
| | Specific serious AEs (≥2% of participants in one of the treatment groups) | X | X |
| Tier 3 | Specific AEs, SOCs or PDLCs‡ (incidence <10% of participants in all of the treatment groups) | | X |
| | Change from Baseline Results (Labs, ECGs, Vital Signs) | | |

‡ Includes only those endpoints not prespecified as Tier 1 or not already prespecified as Tier-2 endpoints.
Note: SOC=System Organ Class; PDLC=Predefined Limit of Change; X = results will be provided.

### 8.6.3 Summaries of Demographic and Baseline Characteristics

The comparability of the treatment groups for each relevant characteristic will be assessed by the use of tables and/or graphs. No statistical hypothesis tests will be performed on these characteristics. The number and percentage of subjects randomized, and the primary reasons for discontinuation will be displayed. Demographic variables (e.g., age, gender) and baseline characteristics will be summarized by treatment either by descriptive statistics or categorical tables.

## 8.7 Interim Analyses

### 8.7.1 Interim Safety Analyses

The DMC will conduct regular safety monitoring. The timing of the safety monitoring will be specified in the DMC Charter. **As of Amendment 06,** no additional eDMC reviews will take place.

### 8.7.2 Interim Efficacy Analyses

**Note: As of Amendment 06, based on the eDMC's recommendation after reviewing IA1 efficacy and safety data, the originally planned IA2 and FA described below will not be performed. The nonbinding futility analysis prespecified at IA2 was performed at IA1 at the recommendation of the eDMC.**

There are 2 planned interim efficacy analyses in addition to the final efficacy analysis for this study.

Interim Analysis 1

The interim analysis 1 (IA1) is an interim analysis for OS. It will be performed when ~ 255 deaths have been observed and ~ 12 months after the last subject randomized, whichever occurs later. An interim analysis of PFS will also be performed at this time. It is estimated that ~ 357 PFS events will have been observed, but there is no requirement for the number of PFS events to proceed with the analysis. IA1 will also be the only analysis for ORR.

Interim Analysis 2

The interim analysis 2 (IA2) is an interim analysis for OS. It will be performed when ~ 307 deaths have been observed and ~ 19 months after the last subject randomized, whichever occurs later. The final analysis of PFS will also be performed at this time. It is estimated that ~ 389 PFS events will have been observed, but there is no PFS event count requirement to proceed with the analysis. A nonbinding futility analysis based on OS may be conducted at IA2. Further details of any futility evaluation will be specified in the sSAP.

Final Analysis

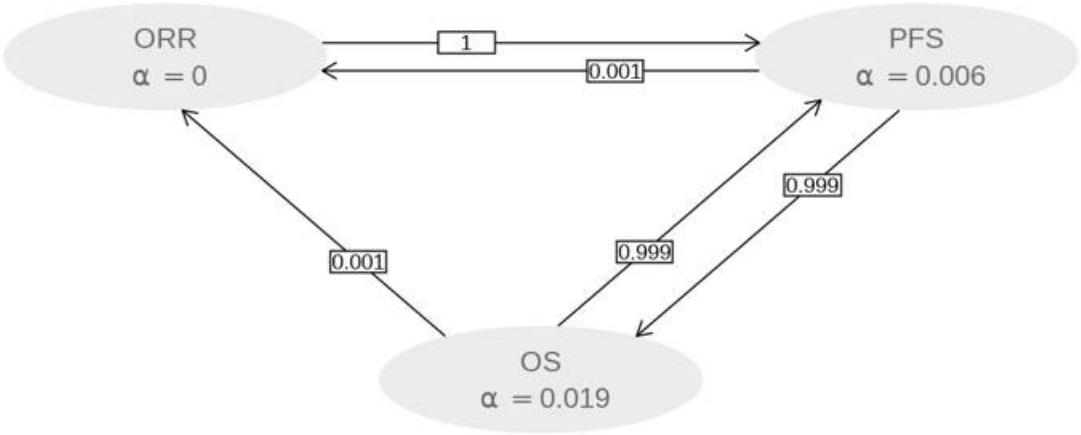
The FA will evaluate OS only. The analysis is planned when ~ 361 deaths have been observed and ~ 27 months after the last subject randomized, whichever occurs later.

The Type I error control for efficacy analyses as well as efficacy bounds are described in Section 8.8 – Multiplicity.

## 8.8 Multiplicity

The overall Type I error rate is strongly controlled at 0.025 (one-sided) α level. The trial uses the graphical method of Maurer and Bretz [41] to provide strong multiplicity control for multiple hypotheses as well as interim analyses. Figure 4 shows the initial one-sided α-allocation for each hypothesis in the ellipse representing the hypothesis. The initial weights for reallocation from each hypothesis to the others are represented in the boxes on the lines connecting hypotheses.

Figure 4 Multiplicity Graph for Type I Error Control




Abbreviations: PFS=progression-free survival; ORR=objective response rate; OS=overall survival.

### 8.8.1 Objective Response Rate

No initial alpha is allocated to test ORR. However, the ORR p-value from IA1 (ie, no new data is added after IA1) can be compared to an α-level of eg, 0.025 if the null hypotheses for both PFS and OS are rejected at IA1 or a later time. The power at the updated α-level of 0.025 is 99.8%, with an approximate treatment difference (ΔORR) required for reaching the efficacy bound being 8.1%, assuming underlying 39% and 59% ORR in the control and experimental groups, respectively.

### 8.8.2 Progression-free Survival

The trial initially allocates α=0.006, one-sided, to test PFS. If the null hypothesis for OS is rejected, its α=0.019 is essentially fully reallocated to PFS hypothesis testing. Thus, the PFS null hypothesis may be tested at α=0.006 or eg. α=0.025 (if both ORR and OS null hypotheses are rejected). Table 15 below shows the boundary properties for each of these α-levels for the IAs and FA, which were derived using a Lan-DeMets O'Brien-Fleming spending function. Note that the final row indicates the total power to reject the null hypothesis for PFS at each α-level. Also note that if the OS null hypothesis is rejected at an IA or FA, each PFS IA and FA test may be compared to its updated bounds considering the α reallocation from the OS hypothesis.

Table 15 Efficacy Boundaries and Properties for Progression-free Survival Analyses

| Analysis | Value | α=0.006 | α=0.025 |
|---|---|---|---|
| IA1: 92% [a] N: 568 Events: 357 Month: ~ 32 [f] | Z | 2.6394 | 2.0667 |
| | p (1-sided)[b] | 0.0042 | 0.0194 |
| | HR at bound[c] | 0.7562 | 0.8034 |
| | P(Cross) if HR=1[d] | 0.0042 | 0.0194 |
| | P(Cross) if HR=0.69[e] | 0.8085 | 0.9251 |
| IA2: Final PFS Analysis N: 568 Events: 389 Month: ~ 39 [f] | Z | 2.5869 | 2.0575 |
| | p (1-sided)[b] | 0.0048 | 0.0198 |
| | HR at bound[c] | 0.7690 | 0.8115 |
| | P(Cross) if HR=1[d] | 0.0060 | 0.0250 |
| | P(Cross) if HR=0.69[e] | 0.8692 | 0.9517 |

[a] Percentage of total planned events at each interim analysis.
[b] The nominal α for testing.
[c] The approximate HR required to reach an efficacy bound
[d] The probability of crossing a bound under the null hypothesis
[e] The probability of crossing a bound under the alternative hypothesis
[f] The approximate number of months since first subject randomized

### 8.8.3 Overall Survival

The OS hypothesis may be tested at α=0.019 or eg. α=0.025 (if both ORR and PFS null hypothese are rejected). Table 16, analogous to the PFS table explained above, demonstrates the boundary properties for each of these α-levels for the IAs and FA, which were derived using a Lan-DeMets O'Brien-Fleming spending function. Note that if the PFS null hypothesis is rejected at an IA, each OS interim and final analysis test may be compared to its updated bounds considering the α reallocation from the PFS hypothesis.

Table 16 Efficacy Boundaries and Properties for Overall Survival Analyses

| Analysis | Value | α=0.019 | α=0.025 |
|---|---|---|---|
| IA1: 71%[a] N: 568 Events: 255 Month: ~ 32 [f] | Z | 2.5592 | 2.4257 |
| | p (1-sided)[b] | 0.0052 | 0.0076 |
| | HR at bound [c] | 0.7256 | 0.7378 |
| | P(Cross) if HR=1[d] | 0.0052 | 0.0076 |
| | P(Cross) if HR=0.7 [e] | 0.6135 | 0.6631 |
| IA2: 85%[a] N: 568 Events: 307 Month: ~ 39 [f] | Z | 2.3490 | 2.2316 |
| | p (1-sided) [b] | 0.0094 | 0.0128 |
| | HR at bound [c] | 0.7646 | 0.7750 |
| | P(Cross) if HR=1[d] | 0.0110 | 0.0151 |
| | P(Cross) if HR=0.7[e] | 0.7900 | 0.8228 |
| FA [g]: N: 568 Events: 361 Month: ~ 47 [f] | Z | 2.1577 | 2.0504 |
| | p (1-sided) [b] | 0.0155 | 0.0202 |
| | HR at bound [c] | 0.7967 | 0.8058 |
| | P(Cross) if HR=1[d] | 0.0190 | 0.0250 |
| | P(Cross) if HR=0.7[e] | 0.8985 | 0.9167 |

[a] Percentage of total planned events at each interim analysis.
[b] The nominal α for testing.
[c] The approximate HR required to reach an efficacy bound
[d] The probability of crossing a bound under the null hypothesis
[e] The probability of crossing a bound under the alternative hypothesis
[f] The approximate number of months since first subject randomized
[g] FA will be conducted at 34 months after the enrollment of the last participant at the latest, if the event accumulation is slower than expected.

The bounds provided in Table 15 and Table 16 are based on the assumption that the expected number of PFS events at IA1 and IA2 (FA for PFS) are 357 and 389, respectively, the number of OS events at IA1, IA2, and FA (FA for OS) are 255, 307, and 361, respectively. At the time of an analysis, the observed number of events may differ substantially from the expected. To avoid overspending at an interim analysis and leave reasonable alpha for the final analysis, the minimum alpha spending strategy will be adopted. At an IA, the information fraction used in Lan-DeMets spending function to determine the alpha spending at the IA will be based on the minimum of the expected information fraction and the actual information fraction at each analysis. Specifically,

- In the scenario that the events accrue slower than expected and the observed number of events is less than the expected number of events at a given analysis, the information fraction will be calculated as the observed number of events at the interim analysis over the target number of events at FA.

- In the scenario that the events accrue faster than expected and the observed number of events exceeds the expected number of events at a given analysis, then the information

fraction will be calculated as the expected number of events at the interim analysis over the target number of events at FA.

The final analysis will use the remaining Type I error that has not been spent at the earlier analyses. The event counts for all analyses will be used to compute correlations.

Of note, while the information fraction used for alpha spending calculation will be the minimum of the actual information fraction and the expected information fraction, the correlations required for deriving the bounds will still be computed using the actual information fraction based on the observed number of events at each analysis over the target number of events at FA.

The minimum spending approach assumes timing is not based on any observed Z-value and thus the Z test statistics used for testing conditioned on timing are multivariate normal. Given the probabilities derived with the proposed spending method, the correlations based on actual event counts are used to compute bounds that control the Type I error at the specified alpha level for a given hypothesis conditioned on the interim analysis timing. Since this is true regardless of what is conditioned on, the overall Type I error for a given hypothesis unconditionally is controlled at the specified level. By using more conservative spending early in the study, power can be retained to detect situations where the treatment effect may be delayed.

### 8.8.4 Safety Analyses

The eDMC has responsibility for assessment of overall risk: benefit. When prompted by safety concerns, the eDMC can request corresponding efficacy data. **As of Amendment 06**, no additional eDMC reviews will take place.

## 8.9 Sample Size and Power Calculations

The study plans to randomize approximately 568 subjects with 1:1 ratio into the pembrolizumab plus ipilimumab arm and the pembrolizumab plus placebo arm.

With 389 PFS events, the study has ~ 87% power for detecting a hazard ratio of 0.69 at 0.60% (one-sided) significance level. With 361 deaths, the study has ~ 90% power for detecting a hazard ratio of 0.7 at 1.90% (one-sided) significance level.

The above sample size and power calculations for PFS and OS assume the following, with control arm assumption estimated from the pembrolizumab arm from KEYNOTE-042 in the PD-L1 TPS ≥50% population:

- PFS follows a piecewise exponential distribution with a median of 6.5 months before 6.5 months and a median of 14.5 months after 6.5 months in the control group.
- OS follows an exponential distribution with a median of 20 months for the control group.
- The HR for PFS and OS between the experimental and control groups is 0.69 and 0.7, respectively.
- Enrollment period of 20 months.
- A yearly dropout rate of 13% and 1% for PFS and OS, respectively.

The sample size and power calculations were performed in the software EAST and R (package "gsDesign").

### 8.10 Subgroup Analyses

To determine whether the treatment effect is consistent across various subgroups, the estimate of the between-group treatment effect (with a nominal 95% CI) for the primary endpoints will be estimated and plotted within each category of the following classification variables:

- ECOG Performance Status (0 versus 1)
- Geographic region (East Asia versus Non-East Asia)
- Histology (squamous versus nonsquamous)
- Age (<65 versus ≥65 years)
- Sex (female versus male)
- Race (white versus non-white)
- Smoking status (never versus former/ current)
- Baseline brain metastasis status (yes versus no)

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

### 8.11 Compliance (Medication Adherence)

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

### 8.12 Extent of Exposure

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

## 9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

### 9.1 Investigational Product

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

**NOTE: As of Amendment 06, ipilimumab and matching placebo have been removed from the study. This section has been updated accordingly.**

Table 17 Product Descriptions

| Product Name & Potency | Dosage Form | Source/Additional Information |
|---|---|---|
| MK-3475 25 mg/mL | Solution for Infusion | Provided centrally by the Sponsor. |

All supplies indicated in Table 17 will be provided per the "Source/Additional Information" column depending on local country operational requirements.

Any commercially available product not included in Table 17 will be provided by the trial site, subsidiary or designee. Every attempt should be made to source these supplies from a single lot/batch number. The trial site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product as per local guidelines unless otherwise instructed by the Sponsor.

## 9.2 Packaging and Labeling Information

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

**NOTE: As of Amendment 06, ipilimumab and matching placebo have been removed from the study. This section has been updated accordingly.**

The open-label pembrolizumab will be provided in 2 vial kits.

## 9.3 Clinical Supplies Disclosure

**NOTE: As of Amendment 06, ipilimumab and matching placebo have been removed from the study. This section is no longer applicable.**

The trial is blinded but supplies are provided open label; therefore, an unblinded pharmacist or qualified trial site personnel will be used to blind supplies. Treatment identity (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

**NOTE: As of Amendment 06, ipilimumab and matching placebo have been removed from the study. This section is no longer applicable.**

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

## 10.0 ADMINISTRATIVE AND REGULATORY DETAILS

### 10.1 Confidentiality

#### 10.1.1 Confidentiality of Data

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

#### 10.1.2 Confidentiality of Subject Records

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

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

#### 10.1.3 Confidentiality of Investigator Information

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

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

2. hospital or clinic address and telephone number;
3. curriculum vitae or other summary of qualifications and credentials; and
4. other professional documentation.

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

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

### 10.1.4 Confidentiality of IRB/IEC Information

The Sponsor is required to record the name and address of each IRB/IEC 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/IEC 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 Protocol/CSR 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 Amendments Act (FDAAA) of 2007 and the European Medicines Agency (EMA) clinical trial Directive 2001/20/EC, the Sponsor of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to http://www.clinicaltrials.gov, www.clinicaltrialsregister.eu or other local registries. 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 FDAAA or the EMA clinical trial directive 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 FDAAA, the EMA clinical trials directive or other locally mandated registries are that of the Sponsor and agrees not to submit any information about this trial or its results to those registries.

## 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] Seymour L, Bogaerts J, Perrone A, Ford R, Schwartz LH, Mandrekar S, et al. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. Lancet Oncol. 2017 Mar;18(3):e143-52.

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

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

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

[5] Talmadge JE, Donkor M, Scholar E. Inflammatory cell infiltration of tumors: Jekyll or Hyde. Cancer Metastasis Rev 2007;26(3-4):373-400.

[6] Usubütün A, Ayhan A, Uygur MC, Özen H, Toklu C, Ruacan S. Prognostic factors in renal cell carcinoma. J Exp Clin Cancer Res 1998;17(1):77-81.

[7] Nobili C, Degrate L, Caprotti R, Franciosi C, Leone BE, Trezzi R, et al. Prolonged survival of a patient affected by pancreatic adenocarcinoma with massive lymphocyte and dendritic cell infiltration after interleukin-2 immunotherapy. Report of a case. Tumori 2008;94(3):426-30.

[8] Leffers N, Gooden MJM, de Jong RA, Hoogeboom B-N, ten Hoor KA, Hollema H, et al. Prognostic significance of tumor-infiltrating T-lymphocytes in primary and metastatic lesions of advanced stage ovarian cancer. Cancer Immunol Immunother 2009;58(3):449-59.

[9] Nishimura H, Honjo T, Minato N. Facilitation of beta selection and modification of positive selection in the thymus of PD-1-deficient mice. J Exp Med. 2000 Mar 6;191(5):891-8.

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

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

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

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

[14] Ropponen KM, Eskelinen MJ, Lipponen PK, Alhava E, Kosma V-M. Prognostic value of tumour-infiltrating lymphocytes (TILs) in colorectal cancer. J Pathol 1997;182(3):318-24.

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

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

[17] Hamid O, Robert C, Daud A, Hodi FS, Hwu WJ, Kefford R, et al. Safety and Tumor Responses with Lambrolizumab (Anti-PD-1) in Melanoma. N Engl J Med 2013;369(2):134-44.

[18] Peters S, Adjei AA, Gridelli C, Reck M, Kerr K, Felip E, et al. Metastatic non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals Oncol 2012;23(Supplement 7):vii56-vii64.

[19] Sandler AB, Nemunaitis J, Denham C, von Pawel J, Cormier Y, Gatzemeier U, et al. Phase III Trial of Gemcitabine Plus Cisplatin Versus Cisplatin Alone in Patients With Locally Advanced or Metastatic Non-Small-Cell Lung Cancer. J Clin Oncol 2000;18(1):122-30.

[20] Zatloukal P, Petruzelka L, Zemanova M, Kolek V, Skrickova J, Pesek M, et al. Gemcitabine plus cisplatin vs. gemcitabine plus carboplatin in stage IIIb and IV non-small cell lung cancer: a phase III randomized trial. Lung Cancer 2003;41(3):321-31.

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

[22] Garon EB, Rizvi NA, Hui R, Leighl N, Balmanoukian AS, Eder JP, et al. Pembrolizumab for the treatment of non-small-cell lung cancer. N Engl J Med. 2015 May 21;372(21):2018-28.

[23] Herbst RS, Baas P, Kim DW, Felip E, Perez-Gracia JL, Han JY, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. Lancet. 2016 Apr 9;387(10027):1540-50.

[24] Reck M, Rodriguez-Abreu D, Robinson AG, Hui R, Csoszi T, Fulop A, et al. Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer. N Engl J Med. 2016 Oct 8. [Epub ahead of print].

[25] Mok TSK, Wu YL, Kudaba I, Kowalski DM, Cho BC, Turna HZ, et al. Final analysis of the phase III KEYNOTE-042 study: pembrolizumab (pembro) versus platinum-based chemotherapy (chemo) as first-line therapy for patients (pts) with PD-L1-positive locally advanced/metastatic NSCLC [abstract]. Presented at: European Lung Cancer Congress (ELCC); 2019 Apr 10-13; Geneva (Switzerland). Ann Oncol. 2019;30(suppl 2):ii38-68. Abstract no. 1020.

[26] Mok TSK, Wu YL, Kudaba I, Kowalski DM, Cho BC, Turna HZ, et al. Final analysis of the phase 3 KEYNOTE-042 study: pembrolizumab vs platinum-based chemotherapy as first-line therapy for patients with PD-L1-positive locally advanced/metastatic NSCLC. Slides presented at: European Lung Cancer Congress (ELCC); 2019 Apr 10-13; Geneva (Switzerland). Abstract no. 1020.

[27] Globocan 2012: Lung Cancer Estimated Incidence, Mortality and Prevalence Worldwide in 2012 [Internet]. Lyon (FR): World Health Organization, International Agency for Research on Cancer (IARC). c2014 – [updated 2014 Oct 3]. Available from: http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx

[28] Socinski M, Creelan B, Horn L, Reck M, Paz-Ares L, Steins M, et al. A phase 3 trial of nivolumab vs investigator s choice (IC) of platinum-based doublet chemotherapy (PT-DC) as first-line therapy for stage iv/recurrent programmed death ligand 1 (PD-L1)−positive NSCLC [abstract]. Abstracts of the 2016 ESMO Congress; 2016 Oct 7-11; Copenhagen; ESMO Congress; 2016. p. 1-3.

[29] Hellmann MD, Rizvi NA, Goldman JW, Gettinger SN, Borghaei H, Brahmer JR, et al. Nivolumab plus ipilimumab as first-line treatment for advanced non-small-cell lung cancer (CheckMate 012): results of an open-label, phase 1, multicohort study. Lancet Oncol. 2016 Dec 2. [Epub ahead of print].

[30] Goldman JW, Antonia SJ, Gettinger SN, Borghaei H, Brahmer JR, Ready NE, et al. Nivolumab (N) plus ipilimumab (I) as first-line (1L) treatment for advanced (adv) NSCLC: 2-yr OS and long-term outcomes from CheckMate 012. Poster session presented at American Society of Clinical Oncology (ASCO), 2017 June 2-6; Chicago, IL.

[31] Long GV, Atkinson V, Cebon JS, Jameson MB, Fitzharris BM, McNeil CM, et al. Pembrolizumab (pembro) plus ipilimumab (ipi) for advanced melanoma: Results of the KEYNOTE-029 expansion cohort. Poster session presented at American Society of Clinical Oncology, 2016 June 3-7; Chicago, IL.

[32] Garassino MC, Gadgeel S, Esteban E, Felip E, Speranza G, Domine M, et al. Patient-reported outcomes following pembrolizumab or placebo plus pemetrexed and platinum in patients with previously untreated, metastatic, non-squamous non-small-cell lung cancer (KEYNOTE-189): a multicentre, double-blind, randomised, placebo-controlled, phase 3 trial. Lancet Oncol. 2020 Mar;21:387-97.

[33] Mazieres J, Kowalski D, Luft A, Vicente D, Tafreshi A, Gumus M, et al. Health-related quality of life with carboplatin-paclitaxel or nab-paclitaxel with or without pembrolizumab in patients with metastatic squamous non-small-cell lung cancer. J Clin Oncol. 2019;38(3):271-80.

[34] Barlesi F, Garon EB, Kim D-W, Felip E, Han J-Y, Kim J-H, et al. Assessment of Health-Related Quality of Life in KEYNOTE-010: A Phase 2/3 Study of Pembrolizumab Versus Docetaxel in Patients With Previously Treated Advanced NSCLC. Poster session Presented at: European Society for Medical Oncology (ESMO) 2016 Congress; 2016 Oct 7-11; Copenhagen, DK.

[35] Brahmer JR, Rodriguez-Abreu D, Robinson AG, Hui R, Csoszi T, Fulop A, et al. Health-related quality of life for pembrolizumab vs chemotherapy in advanced NSCLC with PD-L1 TPS ≥50%: data from KEYNOTE-024. Poster session Presented at: IASLC 17th World Conference on Lung Cancer; 2016 Dec 4-7; Vienna, AT.

[36] Liepa AM, Bushnell DM, Atkinson TM, DeBusk K, McCarrier KP, Martin ML, et al. Evaluating the Non-Small Cell Lung Cancer Symptom Assessment Questionnaire (NSCLC-SAQ): results from the quantitative pilot study. Poster session presented at: IASLC 2016. 17th World Conference on Lung Cancer; 2016 Dec 4-7; Vienna, AT.

[37] McCarrier KP, Atkinson TM, DeBusk KP, Liepa AM, Scanlon M, Coons SJ; Patient-Reported Outcome Consortium, Non–Small Cell Lung Cancer Working Group. Qualitative development and content validity of the Non-small Cell Lung Cancer Symptom Assessment Questionnaire (NSCLC-SAQ), a patient-reported outcome instrument. Clin Ther. 2016 Apr;38(4):794-810.

[38] Wolchok JD, Hoos A, O'Day S, Weber JS, Hamid O, LebbéC, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. Clin Cancer Res 2009;15(23):7412-20.

[39] Hodi FS, Ribas A, Daud A, Hamid O, Robert C, Kefford R, et al. Patterns of response in patients with advanced melanoma treated with Pembrolizumab (MK-3475) and evaluation of immune-related response criteria (irRC). J Immunother Cancer. 2014;2(Suppl 3):P103.

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

[41] Maurer W, Bretz F. Multiple testing in group sequential trials using graphical approaches. Stat Biopharm Res 2013;5(4):311-20.

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

[43] Liang K-Y, Zeger SL. Longitudinal data analysis of continuous and discrete reponses for pre-post designs*. Sankhya: the indian journal of statistics 2000;62:134-48.

# 12.0 APPENDICES

## 12.1 Merck Code of Conduct for Clinical Trials

**Merck***
**Code of Conduct for Clinical Trials**

**I. Introduction**

**A. Purpose**

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

**B. Scope**

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

**II. Scientific Issues**

**A. Trial Conduct**

**1. Trial Design**

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

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

**2. Site Selection**

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

**3. Site Monitoring/Scientific Integrity**

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

**B. Publication and Authorship**

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

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

## III. Subject Protection

### A. IRB/ERC review

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

### B. Safety

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

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

### C. Confidentiality

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

### D. Genomic Research

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

## IV. Financial Considerations

### A. Payments to Investigators

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

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

### B. Clinical Research Funding

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

### C. Funding for Travel and Other Requests

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

## V. Investigator Commitment

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

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

## 12.2 Collection and Management of Specimens for Future Biomedical Research

### 1. Definitions

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

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

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

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

### 2. Scope of Future Biomedical Research

The specimens consented and/or collected in this trial as outlined in Section 7.1.3.5 – Future Biomedical Research Samples will be used in various experiments to understand:

- The biology of how drugs/vaccines work
- Biomarkers responsible for how a drug/vaccine enters and is removed by the body
- Other pathways drugs/vaccines may interact with
- The biology of disease

The specimen(s) may be used for future assay development and/or drug/vaccine development.

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

### 3. Summary of Procedures for Future Biomedical Research

a. Subjects for Enrollment

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

b. Informed Consent

Informed consent for specimens (i.e., DNA, RNA, protein, etc.) will be obtained during screening for protocol enrollment from all subjects or legal guardians, at a trial visit by the investigator or his or her designate. Informed consent for Future Biomedical Research should be presented to the subjects on the visit designated in the trial flow chart. If delayed, present consent at next possible Subject Visit. Consent forms signed by the subject will be kept at the clinical trial site under secure storage for regulatory reasons.

A template of each trial site's approved informed consent will be stored in the Sponsor's clinical document repository.

c. eCRF Documentation for Future Biomedical Research Specimens

Documentation of subject consent for Future Biomedical Research will be captured in the electronic Case Report Forms (eCRFs). Any specimens for which such an informed consent cannot be verified will be destroyed.

d. Future Biomedical Research Specimen(s)

Collection of specimens for Future Biomedical Research will be performed as outlined in the trial flow chart. In general, if additional blood specimens are being collected for Future Biomedical Research, these will usually be obtained at a time when the subject is having blood drawn for other trial purposes.

**4. Confidential Subject Information for Future Biomedical Research**

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

To maintain privacy of information collected from specimens obtained for Future Biomedical Research, the Sponsor has developed secure policies and procedures. All specimens will be single-coded per ICH E15 guidelines as described below.

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

**5. Biorepository Specimen Usage**

Specimens obtained for the Sponsor will be used for analyses using good scientific practices. Analyses utilizing the Future Biomedical Research specimens may be performed by the Sponsor, or an additional third party (e.g., a university investigator) designated by the Sponsor. The investigator conducting the analysis will follow the Sponsor's privacy and confidentiality requirements. Any contracted third party analyses will conform to the specific scope of analysis outlined in future biomedical research protocol and consent. Future Biomedical Research specimens remaining with the third party after specific analysis is performed will be reported to the Sponsor.

**6. Withdrawal From Future Biomedical Research**

Subjects may withdraw their consent for Future Biomedical Research and ask that their biospecimens not be used for Future Biomedical Research. Subjects may withdraw consent at any time by contacting the principal investigator for the main trial. If medical records for the main trial are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@merck.com).

Subsequently, the subject's specimens will be flagged in the biorepository and restricted to main study use only. If specimens were collected from study participants specifically for Future Biomedical Research, these specimens will be removed from the biorepository and destroyed. Documentation will be sent to the investigator confirming withdrawal and/or destruction, if applicable. It is the responsibility of the investigator to inform the subject of completion of the withdrawal and/or destruction, if applicable. Any analyses in progress at the time of request for withdrawal/destruction or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research trial data and results. No new analyses would be generated after the request is received.

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

**7. Retention of Specimens**

Future Biomedical Research specimens will be stored in the biorepository for potential analysis for up to 20 years from the end of the main study. Specimens may be stored for longer if a regulatory or governmental authority has active questions that are being answered. In this special circumstance, specimens will be stored until these questions have been adequately addressed.

Specimens from the trial site will be shipped to a central laboratory and then shipped to the Sponsor-designated biorepository. If a central laboratory is not utilized in a particular trial, the trial site will ship directly to the Sponsor-designated biorepository. The specimens will be stored under strict supervision in a limited access facility which operates to assure the integrity of the specimens. Specimens will be destroyed according to Sponsor policies and procedures and this destruction will be documented in the biorepository database.

**8. Data Security**

Databases containing specimen information and test results are accessible only to the authorized Sponsor representatives and the designated trial administrator research personnel and/or collaborators. Database user authentication is highly secure, and is accomplished using network security policies and practices based on international standards to protect against unauthorized access.

**9. Reporting of Future Biomedical Research Data to Subjects**

No information obtained from exploratory laboratory studies will be reported to the subject, family, or physicians. Principle reasons not to inform or return results to the subject include: Lack of relevance to subject health, limitations of predictive capability, and concerns regarding misinterpretation.

If important research findings are discovered, the Sponsor may publish results, present results in national meetings, and make results accessible on a public website in order to rapidly report this information to doctors and subjects. Subjects will not be identified by

name in any published reports about this study or in any other scientific publication or presentation.

**10. Future Biomedical Research Study Population**

Every effort will be made to recruit all subjects diagnosed and treated on Sponsor clinical trials for Future Biomedical Research.

**11. Risks Versus Benefits of Future Biomedical Research**

For FBR, risks to the subject have been minimized. No additional risks to the subject have been identified as no additional specimens are being collected for FBR (i.e., only leftover samples are being retained).

The Sponsor has developed strict security, policies and procedures to address subject data privacy concerns. Data privacy risks are largely limited to rare situations involving possible breach of confidentiality. In this highly unlikely situation there is risk that the information, like all medical information, may be misused.

**12. Questions**

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

**13. References**

1. National Cancer Institute: http://www.cancer.gov/dictionary/?searchTxt=biomarker
2. International Conference on Harmonization: DEFINITIONS FOR GENOMIC BIOMARKERS, PHARMACOGENOMICS, PHARMACOGENETICS, GENOMIC DATA AND SAMPLE CODING CATEGORIES - E15; http://www.ich.org/LOB/media/MEDIA3383.pdf
3. Industry Pharmacogenomics Working Group. Understanding the Intent, Scope and Public Health Benefits of Exploratory Biomarker Research: A Guide for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/
4. Industry Pharmacogenomics Working Group. Pharmacogenomics Informational Brochure for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/

## 12.3 Eastern Cooperative Oncology Group Performance Status

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

## 12.4 Description of the iRECIST Process for Assessment of Disease Progression

*Assessment at Screening and Prior to RECIST 1.1 Progression*

Until radiographic disease progression based on RECIST 1.1, there is no distinct iRECIST assessment.

*Assessment and Decision at RECIST 1.1 Progression*

For subjects who show evidence of radiological PD by RECIST 1.1 as determined by the investigator, the investigator will decide whether to continue a subject on study treatment until repeat imaging is obtained (using iRECIST for subject management (see Table 8 and Figure 3). This decision by the investigator should be based on the subject's overall clinical condition.

Clinical stability is defined as the following:

- Absence of symptoms and signs indicating clinically significant progression of disease
- No decline in ECOG Performance Status
- No requirements for intensified management, including increased analgesia, radiation, or other palliative care

Any subject deemed clinically unstable should be discontinued from study treatment at site-assessed first radiologic evidence of PD, and is not required to have repeat tumor imaging for confirmation of PD by iRECIST.

If the investigator decides to continue treatment, the subject may continue to receive study treatment and the tumor assessment should be repeated 4 to 8 weeks later to confirm PD by iRECIST, per investigator assessment. Images should continue to be sent in to the central imaging vendor for potential retrospective BICR.

Tumor flare may manifest as any factor causing radiographic progression per RECIST 1.1, including:

- Increase in the sum of diameters of target lesion(s) identified at baseline to ≥20% and ≥5 mm from nadir
    - Note: the iRECIST publication uses the terminology "sum of measurements", but "sum of diameters" will be used in this protocol, consistent with the original RECIST 1.1 terminology.
- Unequivocal progression of nontarget lesion(s) identified at baseline
- Development of new lesion(s)

iRECIST defines new response categories, including iUPD (unconfirmed progressive disease) and iCPD (confirmed progressive disease). For purposes of iRECIST assessment, the first visit showing progression according to RECIST 1.1 will be assigned a visit (overall) response of iUPD, regardless of which factors caused the progression.

At this visit, target and nontarget lesions identified at baseline by RECIST 1.1 will be assessed as usual.

New lesions will be classified as measurable or nonmeasurable, using the same size thresholds and rules as for baseline lesion assessment in RECIST 1.1. From measurable new lesions, up to 5 lesions total (up to 2 per organ), may be selected as New Lesions – Target. The sum of diameters of these lesions will be calculated, and kept distinct from the sum of diameters for target lesions at baseline. All other new lesions will be followed qualitatively as New Lesions – Nontarget.

*Assessment at the Confirmatory Imaging*

On the confirmatory imaging, the subject will be classified as progression confirmed (with an overall response of iCPD), or as showing persistent unconfirmed progression (with an overall response of iUPD), or as showing disease stability or response (iSD/iPR/iCR).

*Confirmation of Progression*

Progression is considered confirmed, and the overall response will be iCPD, if ANY of the following occurs:

- Any of the factors that were the basis for the initial iUPD show worsening
    - For target lesions, worsening is a further increase in the sum of diameters of ≥5 mm, compared to any prior iUPD time point
    - For nontarget lesions, worsening is any significant growth in lesions overall, compared to a prior iUPD time point; this does not have to meet the "unequivocal" standard of RECIST 1.1
    - For new lesions, worsening is any of these:
        - An increase in the new lesion sum of diameters by ≥5 mm from a prior iUPD time point
        - Visible growth of new nontarget lesions
        - The appearance of additional new lesions
- Any new factor appears that would have triggered PD by RECIST 1.1

*Persistent iUPD*

Progression is considered not confirmed, and the overall response remains iUPD, if:

- None of the progression-confirming factors identified above occurs AND
- The target lesion sum of diameters (initial target lesions) remains above the initial PD threshold (by RECIST 1.1)

Additional imaging for confirmation should be scheduled 4 to 8 weeks from the imaging on which iUPD is seen. This may correspond to the next visit in the original visit schedule. The assessment of the subsequent confirmation imaging proceeds in an identical manner, with possible outcomes of iCPD, iUPD, and iSD/iPR/iCR.

*Resolution of iUPD*

Progression is considered not confirmed, and the overall response becomes iSD/iPR/iCR, if:

- None of the progression-confirming factors identified above occurs, AND
- The target lesion sum of diameters (initial target lesions) is not above the initial PD threshold.

The response is classified as iSD or iPR (depending on the sum of diameters of the target lesions), or iCR if all lesions resolve.

In this case, the initial iUPD is considered to be pseudoprogression, and the level of suspicion for progression is "reset". This means that the next visit that shows radiographic progression, whenever it occurs, is again classified as iUPD by iRECIST, and the confirmation process is repeated before a response of iCPD can be assigned.

*Management Following the Confirmatory Imaging*

If repeat imaging does not confirm PD per iRECIST, as assessed by the investigator, and the subject continues to be clinically stable, study treatment may continue and follow the regular imaging schedule. If PD is confirmed, subjects will be discontinued from study treatment.

NOTE: If a subject has confirmed radiographic progression (iCPD) as defined above, but the subject is achieving a clinically meaningful benefit, an exception to continue study treatment may be considered following consultation with the Sponsor. In this case, if study treatment is continued, tumor imaging should continue to be performed following the intervals as outlined in the Trial Flow Chart in Section 6. and submitted to the central imaging vendor.

*Detection of Progression at Visits After Pseudo-progression Resolves*

After resolution of pseudoprogression (ie, achievement of iSD/iPR/iCR), iUPD is indicated by any of the following events:

- Target lesions
  - Sum of diameters reaches the PD threshold (≥20% and ≥5 mm increase from nadir) either for the first time, or after resolution of previous pseudoprogression. The nadir is always the smallest sum of diameters seen during the entire trial, either before or after an instance of pseudoprogression.
- Nontarget lesions
  - If nontarget lesions have never shown unequivocal progression, their doing so for the first time results in iUPD.
  - If nontarget lesions have shown previous unequivocal progression, and this progression has not resolved, iUPD results from any significant further growth of nontarget lesions, taken as a whole.
- New lesions
  - New lesions appear for the first time
  - Additional new lesions appear

- Previously identified new target lesions show an increase of ≥ 5 mm in the new lesion sum of diameters, from the nadir value of that sum
- Previously identified nontarget lesions show any significant growth

If any of the events above occur, the overall response for that visit is iUPD, and the iUPD evaluation process (see Assessment at the Confirmatory Imaging above) is repeated. Progression must be confirmed before iCPD can occur.

The decision process is identical to the iUPD confirmation process for the initial PD, with one exception: if new lesions occurred at a prior instance of iUPD, and at the confirmatory imaging the burden of new lesions has increased from its smallest value (for new target lesions, the sum of diameters is ≥5 mm increased from its nadir), then iUPD cannot resolve to iSD or iPR. It will remain iUPD until either a decrease in the new lesion burden allows resolution to iSD or iPR, or until a confirmatory factor causes iCPD.

Additional details about iRECIST are provided in the iRECIST publication [1].

## 12.5 Contraceptive Guidance and Pregnancy Testing

**Woman of Childbearing Potential (WOCBP)**

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

Women in the following categories are not considered WOCBP:

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

  Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with 2 FSH measurements in the postmenopausal range is required.
  - Females on HRT and whose menopausal status is in doubt will be required to use one of the nonhormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

**Contraception Requirements**

**Male Participants:**

**NOTE: As of amendment 06, contraception is no longer required for male participants. Sperm donation is also acceptable.**

Male participants with female partners of childbearing potential are eligible to participate if they agree to one of the following during the protocol defined time frame in Section 5.1.2:

- Be abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent
- Use a male condom plus partner use of a contraceptive method with a failure rate of <1% per year as described in Table 18 when having penile-vaginal intercourse with a WOCBP who is not currently pregnant.

- Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration.

**Female Participants:**

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in Table 18 during the protocol-defined time frame in Section 5.1.2.

Table 18 Highly Effective Contraception Methods

| |
|---|
| **Highly Effective Contraceptive Methods That Are User Dependent** [a]<br>*Failure rate of <1% per year when used consistently and correctly.* |
| ● Combined (estrogen- and progestogen- containing) hormonal contraception [b, c]<br>○ Oral<br>○ Intravaginal<br>○ Transdermal<br>○ Injectable |
| ● Progestogen-only hormonal contraception [b, c]<br>○ Oral<br>○ Injectable |
| **Highly Effective Methods That Have Low User Dependency**<br>*Failure rate of <1% per year when used consistently and correctly.* |
| ● Progestogen- only contraceptive implant [b, c]<br>● Intrauterine hormone-releasing system (IUS) [b]<br>● Intrauterine device (IUD)<br>● Bilateral tubal occlusion |
| ● **Vasectomized partner**<br>A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. |
| ● **Sexual abstinence**<br>Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.) |
| Notes:<br>Use should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies.<br><br>a) Typical use failure rates are higher than perfect-use failure rates (i.e. when used consistently and correctly).<br>b) If hormonal contraception efficacy is potentially decreased due to interaction with study treatment, condoms must be used in addition to the hormonal contraception during the treatment period and for at least 120 days, corresponding to time needed to eliminate study treatment plus 30 days for study treatments with genotoxic potential after the last dose of study treatment.<br>c) If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable hormonal contraceptives are limited to those which inhibit ovulation. |

### Pregnancy Testing

WOCBP should only be included after a negative highly sensitive serum pregnancy test.

Following initiation of treatment, pregnancy testing will be performed whenever an expected menstrual cycle is missed or when pregnancy is otherwise suspected; at the time points specified in the Schedule of Activities, and as required locally.

Pregnancy testing will be performed whenever an expected menstrual cycle is missed or when pregnancy is otherwise suspected.

## 12.6 List of Abbreviations

| Abbreviation/Term | Definition |
|---|---|
| 1L | first-line |
| 3X | 3 times |
| ACTH | adrenocorticotropic hormone |
| AE | adverse event |
| AEOSI | adverse event of special interest |
| ADA | antidrug antibodies |
| ALT | alanine aminotransferase |
| ALK | anaplastic lymphoma kinase |
| aPTT | activated partial thromboplastin time |
| ASaT | All Subjects as Treated |
| ASCO | American Society of Clinical Oncologists |
| AST | aspartate aminotransferase |
| β-hCG | beta-human chorionic gonadotropin |
| BCG | Bacillus Calmette-Guérin |
| BICR | blinded independent central review |
| CBC | complete blood count |
| CI | confidence interval |
| cLDA | constrained longitudinal data analysis |
| $C_{max}$ | serum maximum concentration |
| CR | complete response |
| CrCl | calculated creatinine clearance |
| C-Path | Critical Path Institute |
| CT | computed tomography |
| CTCAE | Common Terminology Criteria for Adverse Events |
| DMC | Data Monitoring Committee |
| DNA | deoxyribonucleic acid |
| DOR | duration of response |
| ECIs | events of clinical interest |
| ECG | electrocardiogram |
| ECOG | Eastern Cooperative Oncology Group |
| eCRF | electronic case report form |
| EDC | electronic data capture |
| EGFR | epidermal growth factor receptor |
| EMA | European Medicines Agency |
| EOC | Executive Oversight Committee |
| EOI | end of infusion |
| EORTC | European Organization for Research and Treatment of Cancer |
| EQ-5D-5L | EuroQol 5-dimension, 5-level Questionnaire |
| ERC | Ethics Review Committee |
| FA | final analysis |
| FBR | Future Biomedical Research |
| FDA | Food and Drug Administration |

| Abbreviation/Term | Definition |
|---|---|
| FFPE | formalin-fixed, paraffin-embedded |
| FSH | follicle-stimulating hormone |
| FT3/T3 | Free triiodothyronine |
| FT4/T4 | Free thyroxine |
| GCP | Good Clinical Practice |
| GFR | glomerular filtration rate |
| HCV | hepatitis c virus |
| HIV | human immunodeficiency virus |
| HR | hazard ratio |
| IA1 | interim analysis 1 |
| IA2 | interim analysis 2 |
| IB | Investigator's brochure |
| ICH | International Conference on Harmonisation |
| IHC | immunohistochemistry |
| INR | international normalized ratio |
| IC | investigator's choice |
| IRB | Institutional Review Board |
| iCPD | iRECIST confirmed progressive disease |
| iCR | iRECIST complete response |
| iCRO | imaging clinical research organization |
| iPR | iRECIST partial response |
| irAE | immune-related AE |
| iRECIST | modified Response Evaluation Criteria in Solid Tumors 1.1 for immune-based therapeutics |
| iSD | iRECIST stable disease |
| iUPD | iRECIST unconfirmed progressive disease; |
| ITT | intent-to-treat |
| IV | intravenous |
| IVRS | interactive voice response system |
| IWRS | integrated web response system |
| MRI | magnetic resonance imaging |
| MSD | Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. |
| NCI | National Cancer Institute |
| NSCLC | nonsmall cell lung cancer |
| NSCLC-SAQ | The Non-small Cell Lung Cancer Symptom Assessment Questionnaire |
| ORR | objective response rate |
| OS | overall survival |
| OTC | over-the-counter |
| PD | progressive disease |
| PD-1 | programmed cell death protein-1 |
| PD-L1 | programmed death-ligand 1 |
| PD-L2 | programmed death-ligand 2 |
| PFS | progression-free survival |

| Abbreviation/Term | Definition |
|---|---|
| PBPK | physiologically-based pharmacokinetic |
| PGIC-LC | Patient Global Impression of Change – Lung Cancer Symptoms questionnaires |
| PGIS-LC | Patient Global Impression of Severity – Lung Cancer Symptoms Questionnaire |
| PGIC-L | Patient Global Impression of Change – Lung Symptoms Questionnaire |
| PK | pharmacokinetic |
| PO | oral |
| PRO | patient-reported outcome |
| PR | partial response |
| PS | performance scale |
| PT | prothrombin time |
| QLQ-LC13 | Quality of Life Questionnaire and Lung Cancer Module 13 |
| QLQ-C30 | Quality of Life Questionnaire Core 30 |
| QoL | quality of life |
| Q2W | every 2 weeks |
| Q3W | every 3 weeks |
| Q6W | every 6 weeks |
| Q12W | every 12 weeks |
| RCC | renal cell carcinoma |
| RNA | ribonucleic acid |
| RECIST | Response Evaluation Criteria in Solid Tumors Version 1.1 |
| RMST | restricted mean survival time |
| RR | response rate |
| SAE | serious adverse events |
| SAP | Statistical Analysis Plan |
| SD | stable disease |
| SGOT | serum glutamic oxaloacetic transaminase |
| SGPT | serum glutamic pyruvic transaminase |
| SIM | Site Imaging Manual |
| SOC | standard of care |
| sSAP | supplemental statistical analysis plan |
| TMDD | target-mediated drug disposition |
| TTD | time to true deterioration |
| TPS | tumor proportion score |
| TRAEs | treatment-related adverse events |
| TSH | thyroid stimulating hormone |
| ULN | upper limit of normal |
| US | United States |
| USPI | United States Package Insert |
| VOP | verification of progression |
| WOCBP | women of childbearing potential |

## 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 – TRIAL PROCEDURES (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 | |