Official Protocol Title:	A Randomized, Open Label, Phase III Study of Overall Survival Comparing Pembrolizumab (MK-3475) versus Platinum Based Chemotherapy in Treatment Naïve Subjects with PD-L1 Positive Advanced or Metastatic Non-Small Cell Lung Cancer (Keynote 042)
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TITLE:

A Randomized, Open Label, Phase III Study of Overall Survival Comparing Pembrolizumab (MK-3475) versus Platinum Based Chemotherapy in Treatment Naïve Subjects with PD-L1 Positive Advanced or Metastatic Non-Small Cell Lung Cancer (Keynote 042)

IND NUMBER: 116833
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SUMMARY OF CHANGES

PRIMARY REASON(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
5.2.1.2	Dose Modification	The dose modification guidelines are expanded to cover supportive care, monitoring, and follow-up. Myocarditis is added.	To provide current, comprehensive guidelines for management of immune-related adverse events.
6.1	Pembrolizumab Arm: Treatment and Follow-up Phase	Survival status activities may take place throughout the trial. The frequency of telephone contacts during the Survival Follow-up Phase is changed from every 2 months to approximately every 2 months.	To enable flexibility of survival status activities and ensure that current, complete survival data are available at the time of database locks.
6.2	Standard of Care Arm: Treatment and Follow-up Phase		
6.3	Second Course Treatment and Follow-up Phase for Pembrolizumab Arm		
7.1.5.4.2	Survival Follow-up	The frequency of telephone contacts during the Survival Follow-up Phase is changed from every 2 months to approximately every 2 months.	To enable flexibility of survival status activities.
7.1.5.6	Survival Status	This section is added to state that the Sponsor may request updated survival data during the course of the trial.	To enable flexibility of survival status activities and ensure that current, complete survival data are available at the time of database locks.

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
8.0	Statistical Analysis Plan	[redacted]	[redacted]
		[redacted]	[redacted]
		PFS hypotheses will be tested at both interim analyses and final analysis.	To achieve sufficient follow-up duration for PFS.

ADDITIONAL CHANGE(S) FOR THIS AMENDMENT:

Section Number	Section Title	Description of Change(s)	Rationale
2.1	Trial Design	Serious adverse events (SAEs) and Events of Clinical Interest (ECI) 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.	Correction of typographic error.
		[redacted]	
4.2.2	Rationale for Dose Selection/Regimen/ Modification	The rationale for the pembrolizumab dose of 200 mg every 3 weeks was updated.	Updated clinical and pharmacology data are available.
6.1	Pembrolizumab Arm: Treatment and Follow-up Phase	Pharmacokinetics and anti-pembrolizumab antibodies are removed from the trial flow chart.	Pharmacokinetic and anti-drug antibody data have allowed adequate characterization of the clinical pharmacology of pembrolizumab.
7.1.3	Laboratory Procedures/Assessments	Determination of pharmacokinetics and anti-pembrolizumab antibodies is discontinued.	

1.0 TRIAL SUMMARY

Abbreviated Title	OS Study of Pembrolizumab (MK-3475) vs. SOC in Treatment Naïve Subjects with PD-L1 Positive Advanced or Metastatic NSCLC (Keynote 042)
Trial Phase	Phase III
Clinical Indication	PD-L1 positive (TPS≥1%), previously untreated advanced or metastatic non-small cell lung cancer (NSCLC)
Trial Type	Interventional
Type of control	Active control without placebo
Route of administration	Intravenous
Trial Blinding	Unblinded Open-label
Treatment Groups	Pembrolizumab (MK-3475) 200 mg intravenous (IV) every 3 weeks (Q3W) **OR** SOC: investigator's choice of one of the following: --Carboplatin AUC 5 or 6 + paclitaxel 200 mg/m^2 Q3W for a maximum of 6 cycles, followed by optional pemetrexed 500 mg/m^2 for subjects with non-squamous histologies --Carboplatin AUC 5 or 6 + pemetrexed 500 mg/m^2 Q3W for a maximum of 6 cycles, followed by optional pemetrexed 500 mg/m^2 for subjects with non-squamous histologies
Number of trial subjects	Global Study: Approximately 1240 subjects will be enrolled.
Estimated duration of trial	Global Study: The sponsor estimates that the trial will require approximately 3.5 years from the time the first subject signs the informed consent until the last subject's last visit.
Duration of Participation	Each subject will participate in the trial for approximately 2.5 years from the time the subject signs the Informed Consent Form (ICF) through the final contact. After a Screening Phase of up to 42 days, each subject will receive treatment based on the arm to which they have been randomized. Treatment on study will continue until disease progression, unacceptable adverse event(s), intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw the subject, noncompliance with trial treatment or procedures requirements, the subject receives 35 treatments of study medication (pembrolizumab arm only), or administrative reasons. Subjects on the pembrolizumab arm who attain a complete response may consider stopping trial treatment if they meet criteria for holding therapy. Subjects receiving pembrolizumab who stop drug administration after receiving 35 trial treatments for reasons other than disease progression or intolerability, or subjects who attain a complete response and stop trial treatment may be eligible for retreatment with pembrolizumab upon experiencing disease progression. The decision to retreat will be at the discretion of the investigator only if they meet the criteria for retreatment and the trial is ongoing. After the end of treatment each subject will be followed for a minimum of 30 days for adverse event (AE) monitoring. Serious adverse events (SAE) and Events of Clinical Interest (ECI) 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. Subjects who discontinue for reasons other than disease progression will be monitored for disease status in the Observation Phase until disease progression is confirmed by the site, a non-study cancer treatment is initiated, consent is withdrawn, or the subject is lost to follow-up. All subjects will be followed by telephone for overall survival until death, withdrawal of consent, or end of the study.
Randomization Ratio	1:1

A list of abbreviations used in this document can be found in Section 12.7

2.0 TRIAL DESIGN

2.1 Trial Design

This is a multicenter, international, randomized, open-label, controlled trial of IV pembrolizumab (also known as MK-3475) monotherapy versus (vs.) standard of care (SOC) platinum-based chemotherapy in subjects previously untreated for their advanced or metastatic, PD-L1 positive (TPS≥1% [tumor proportion score]) NSCLC. To target approximately 530 subjects with TPS≥50%, approximately 1240 NSCLC subjects whose tumors are classified as TPS≥1% and in whom EGFR or ALK-directed therapy is not indicated. NSCLC subjects are projected to be enrolled in this trial for examination of the efficacy and safety of pembrolizumab vs. SOC chemotherapy. Subjects will be randomized 1:1 to receive pembrolizumab 200 mg IV Q3W or the investigator's choice of one of the platinum doublets specified below. The platinum doublet (including whether pemetrexed maintenance will be offered for those subjects with non-squamous histologies and who do not demonstrate PD after completion of at least 4 cycles of platinum doublet) as well as the dose (for example, AUC 5 OR 6 for carboplatin) to be administered must be identified prior to randomization:

1. Carboplatin AUC 5 or 6 Day 1 Q3W in combination with paclitaxel 200 mg/m^2 Q3W for a maximum of 6 cycles followed by optional pemetrexed 500 mg/m^2 Q3W.

2. Carboplatin AUC 5 or 6 Day 1 Q3W in combination with pemetrexed 500 mg/m^2 Q3W for a maximum of 6 cycles followed by optional pemetrexed 500 mg/m^2 Q3W.

Only subjects with non-squamous histologies may receive pemetrexed. Pemetrexed maintenance is limited to subjects with non-squamous histologies who experience a stable disease (SD) or better after completion of a minimum of 4 cycles of the initial platinum doublet. Subjects who experience progressive disease (PD) after 4 cycles are not permitted to receive pemetrexed in the maintenance setting. Note: While pemetrexed maintenance is optional, it is STRONGLY recommended in subjects with non-squamous histologies and should be administered unless toxicity or decline in performance status precludes its administration, and radiographic imaging does not demonstrate PD after completion of at least 4 cycles of platinum doublet.

Subjects who received adjuvant therapy are permitted onto the study if completion of the adjuvant therapy was completed at least 6 months prior to the development of metastatic disease. If a subject received either carboplatin in combination with pemetrexed OR carboplatin in combination with paclitaxel in the adjuvant setting, that same platinum doublet may not be administered if the subject is randomized to the control arm.

Subjects will be stratified by Eastern Cooperative Oncology Group (ECOG) Performance Scale (0 vs. 1), histology (squamous vs. non-squamous), geographic region of the enrolling site (East Asia vs. non-East Asia), and PD-L1 expression status (TPS ≥50% vs. TPS 1-49%) prior to randomization.

Subjects will be evaluated every 9 weeks (63 ± 7 days) with radiographic imaging to assess response to treatment; treatment-based decisions should be based on the modified RECIST 1.1 criteria (details are provided in the Image Acquisition Guidelines). All imaging obtained on study will be submitted for a central independent radiologists' review that will assess the images using Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 for determination of objective response rate (ORR) and progression-free survival (PFS). Adverse event (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 have been administered, documented disease progression, unacceptable adverse event(s), intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw the subject, subject withdraws consent, pregnancy of the subject, noncompliance with trial treatment or procedure requirements, or administrative reasons.

Pembrolizumab-treated subjects, who attain a confirmed complete response (CR) per modified RECIST 1.1 or who stop trial treatment after 35 administrations of study medication for reasons other than disease progression or intolerability, may consider stopping trial treatment. These subjects may be eligible for re-treatment with pembrolizumab monotherapy after they have experienced radiographic disease progression at the discretion of the investigator according to defined criteria in Section 7.1.5.5; this re-treatment will be the Second Course Phase. Response or progression in the Second Course Phase will not count towards the ORR and PFS endpoints in this trial.

After the end of treatment, each subject will be followed for a minimum of 30 days for AE monitoring. Serious adverse events (SAEs) and Events of Clinical Interest (ECI) 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. Subjects will have post-treatment follow-up for disease status, including initiating a non-study cancer treatment and experiencing disease progression, until death, withdrawing consent, or becoming lost to follow-up.

The primary endpoint of the trial is Overall Survival (OS) in subjects with TPS≥50%, TPS≥20%, and TPS≥1%. Secondary endpoints include PFS and ORR per RECIST 1.1 by central independent radiologists' review in subjects with TPS≥50%, TPS≥20%, and TPS≥1%, and safety as assessed by a variety of parameters of AEs, including ECIs with a

potential immunologic etiology as outlined in the ECI guidance document. Exploratory analyses include response duration per RECIST 1.1 by central independent radiologists' review in subjects with TPS≥50%, TPS≥20%, and TPS≥1%, PFS and ORR per RECIST 1.1 by investigator review in subjects with TPS≥50%, TPS≥20%, and TPS≥1.

Participation in this trial will be dependent upon supplying tumor tissue from locations not radiated prior to biopsy; formalin-fixed specimens AFTER the subject has been diagnosed with metastatic disease will be required for determination of PD-L1 status prior to randomization. Biopsies obtained PRIOR to receipt of adjuvant chemotherapy are NOT permitted. Subjects who received adjuvant therapy are permitted onto the trial as long as therapy was completed at least 6 months prior to the diagnosis of metastatic disease.

The specimen will be evaluated at a central laboratory facility for expression status of PD-L1 in a prospective manner. Only subjects whose tumors express PD-L1 at a predefined cut point as determined by the central laboratory facility will be eligible for randomization.

[redacted] in both arms in the subjects with TPS≥50% and at least 6 months after the last patient is enrolled. The main purpose of this analysis is to demonstrate superiority of pembrolizumab in OS. The second interim analysis (IA2) will be conducted approximately 38 months [redacted] after enrollment completion. [redacted]. In addition, the trial may be stopped early at the recommendation of the Data Monitoring Committee (DMC) if the risk/benefit ratio to the trial population as a whole is unacceptable. Details are described in Section 8.0 – Statistical Analysis Plan.

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

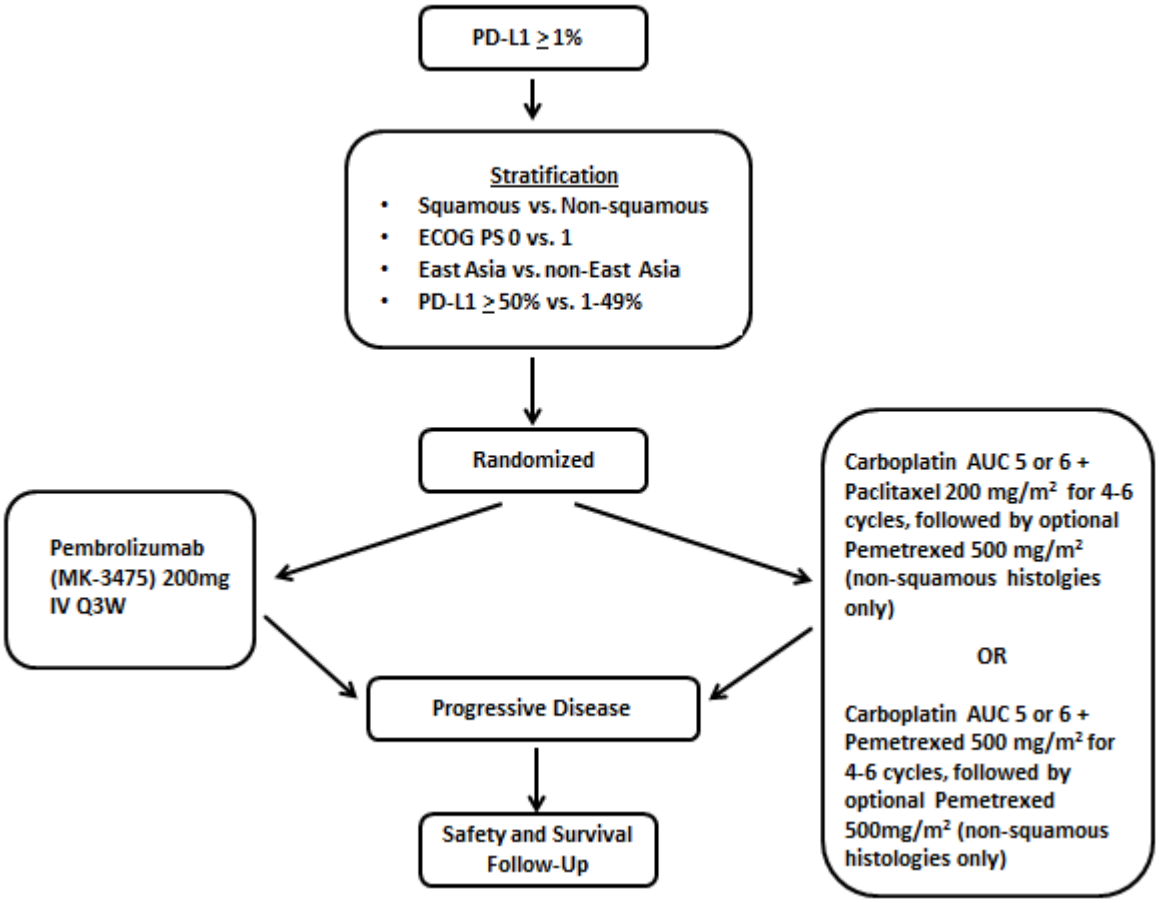

Figure 1 Trial Diagram

3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

3.1 Primary Objective(s) & Hypothesis(es)

1. **Objective:** To compare the overall survival (OS) in subjects with TPS≥50%, 1L advanced/metastatic NSCLC treated with pembrolizumab compared to standard of care (SOC) chemotherapies.

   Hypothesis: Pembrolizumab prolongs OS in subjects with TPS≥50%, NSCLC compared to SOC chemotherapy.

2. **Objective:** To compare the OS in subjects with TPS≥20%, 1L advanced/metastatic NSCLC treated with pembrolizumab compared to standard of care (SOC) chemotherapies.

   Hypothesis: Pembrolizumab prolongs OS in subjects with TPS≥20% NSCLC compared to SOC chemotherapy.

3. **Objective:** To compare the OS in subjects with TPS≥1%, 1L advanced/metastatic NSCLC treated with pembrolizumab compared to SOC chemotherapies.

   Hypothesis: Pembrolizumab prolongs OS in subjects with TPS≥1% NSCLC compared to SOC chemotherapy.

The study is considered to have met its primary objective if pembrolizumab is superior to SOC in OS at an interim analysis or the final analysis in the subjects with TPS≥50%.

3.2 Secondary Objective(s) & Hypothesis(es)

1. **Objective:** To compare the progression-free survival (PFS) by RECIST 1.1 as assessed by central independent radiologists' review in subjects with TPS≥50%, 1L advanced/metastatic NSCLC treated with pembrolizumab compared to SOC chemotherapy.

   Hypothesis: Pembrolizumab prolongs PFS by RECIST 1.1 (central independent radiologists' review) in subjects with TPS≥50% NSCLC compared to SOC chemotherapy.

2. **Objective:** To compare the PFS by RECIST 1.1 as assessed by central independent radiologists' review in subjects with TPS≥20%, 1L advanced/metastatic NSCLC treated with pembrolizumab compared to SOC chemotherapy.

   Hypothesis: Pembrolizumab prolongs PFS by RECIST 1.1 (central independent radiologists' review) in subjects with TPS≥20% NSCLC compared to SOC chemotherapy.

3. **Objective:** To compare the PFS as assessed by RECIST 1.1 by central independent radiologists' review in subjects with TPS≥1%, 1L advanced/metastatic NSCLC treated with pembrolizumab compared to SOC chemotherapy.

   Hypothesis: Pembrolizumab prolongs PFS by RECIST 1.1 (central independent radiologists' review) in subjects with TPS≥1% NSCLC compared to SOC chemotherapy.

4. **Objective:** To evaluate the ORR by RECIST 1.1 by central independent radiologists' review in subjects with TPS≥50%, 1L advanced/metastatic NSCLC treated with pembrolizumab compared to SOC chemotherapy.

   Hypothesis: Pembrolizumab improves ORR by RECIST 1.1 (central independent radiologists' review) in subjects with TPS≥50% NSCLC compared to SOC chemotherapy.

5. **Objective:** To evaluate the ORR by RECIST 1.1 by central independent radiologists' review in subjects with TPS≥20%, 1L advanced/metastatic NSCLC treated with pembrolizumab compared to SOC chemotherapy.

   Hypothesis: Pembrolizumab improves ORR by RECIST 1.1 (central independent radiologists' review) in subjects with TPS≥20% NSCLC compared to SOC chemotherapy.

6. **Objective:** To evaluate the ORR by RECIST 1.1 by central independent radiologists' review in subjects with TPS≥1%, 1L advanced/metastatic NSCLC treated with pembrolizumab compared to SOC chemotherapy.

   Hypothesis: Pembrolizumab improves ORR by RECIST 1.1 (central independent radiologists' review) in subjects with TPS≥1% NSCLC compared to SOC chemotherapy.

7. **Objective:** To evaluate the safety and tolerability profile of pembrolizumab in subjects with TPS ≥1%, 1L advanced/metastatic NSCLC.

3.3 Exploratory Objectives

- **Objective:** To evaluate PFS per investigator-assessed RECIST 1.1 response criteria in subjects with TPS≥50%, TPS≥20%, and TPS≥1%, 1L advanced/metastatic NSCLC treated with pembrolizumab compared to SOC chemotherapy.

- **Objective:** To evaluate ORR per investigator-assessed RECIST 1.1 response criteria in subjects with TPS≥50%, TPS≥20%, and TPS≥1%, 1L advanced/metastatic NSCLC treated with pembrolizumab compared to SOC chemotherapy.

- **Objective:** To evaluate response duration per RECIST 1.1 by central independent radiologists' review in subjects with TPS≥50%, TPS≥20%, and TPS≥1%, 1L advanced/metastatic NSCLC treated with pembrolizumab compared to SOC chemotherapy**.**

- **Objective:** To evaluate the PFS as assessed by RECIST 1.1 by investigator review in the next line of therapy (PFS2) in subjects treated with pembrolizumab compared to SOC chemotherapy.

- **Objective**: To evaluate genomic signatures that predict for response in subjects treated with pembrolizumab.

- **Objective:** To investigate the relationship between pembrolizumab treatment and biomarkers predicting response (e.g., PD-L1, genetic variation, serum sPDL1) utilizing newly obtained or archival FFPE tumor tissue and blood, including serum and plasma.

4.0 BACKGROUND & RATIONALE

4.1 Background

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

4.1.1 Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades [1]. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies [2] [3] [3] [4] [5] [6] [7] [8] [9] [10] [11] [12] [13] [14] [15] [16] [17] [18] [19] [20] [21] [22] [23] [24] [25] [26] [27] [28] [29] [30] [31] [32] [33] [34] [35] [36] [37]. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells/FoxP3+ regulatory T-cells seems to correlate with improved prognosis and long-term survival in solid malignancies such as ovarian, colorectal and pancreatic cancer, hepatocellular carcinoma, malignant melanoma (MEL) and renal cell carcinoma (RCC). TILs can be expanded ex vivo and re-infused, inducing durable objective tumor responses in cancers such as MEL [38] [39].

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an Ig superfamily member related to CD28 and CTLA-4 which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) [40] [41]. The mechanism by which PD-1 down modulates T-cell responses is similar to, but distinct from that of CTLA-4, as both molecules regulate an overlapping set of signaling proteins [34] [42]. PD-1 was shown to be expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B-cells, T regs and Natural Killer cells [43] [44]. The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types, including non-hematopoietic tissues as well as in various tumors [42] [45] [46] [47]. Both ligands are type I transmembrane receptors containing both IgV- and IgC-like domains in the extracellular region and contain short cytoplasmic regions with no known signaling motifs. Binding of either PD-1 ligand to PD-1 inhibits T-cell activation triggered through the T-cell receptor. PD-L1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments. PD-L2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T-cell function in peripheral tissues [45]. Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. High expression of PD-L1 on tumor cells (and to a lesser extent of PD-L2) has been found to correlate with poor prognosis and survival in various cancer types, including RCC [48], pancreatic carcinoma [49], hepatocellular carcinoma [50], and ovarian carcinoma [51]. Furthermore, PD-1 has been suggested to regulate tumor-specific T-cell expansion in subjects with MEL [52].

PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention. The prognostic implications of PD-L1 expression in NSCLC are currently being investigated in ongoing epidemiologic studies as well as Keynote 001 and Keynote 010, the Phase II/III trial of pembrolizumab vs. docetaxel in previously treated subjects with advanced or metastatic NSCLC.

Anti-mouse PD-1 or anti-mouse PD-L1 antibodies have demonstrated anti-tumor responses as a monotherapy in models of squamous cell carcinoma, pancreatic carcinoma, MEL, and colorectal carcinoma. Blockade of the PD-1 pathway effectively promoted CD8+ T-cell infiltration into the tumor and the presence of IFN-γ, granzyme B and perforin, indicating that the mechanism of action involved local infiltration and activation of effector T-cell function in vivo [49] [53] [54] [55] [56] [57]. In addition, the combination of gemcitabine and anti-PD-L1 mAb demonstrated synergy in the rejection of pancreatic mouse tumors [49]. In-house experiments have confirmed the in vivo efficacy of PD-1 blockade as a monotherapy as well as in combination with chemotherapy in syngeneic mouse tumor models (see the IB).

Recent clinical data of pembrolizumab suggest high sustained rates of tumor regression in patients with advanced melanoma. Pembrolizumab was dosed IV at a dose of 10 mg per kilogram (kg) of body weight every 2 or 3 weeks or 2 mg per kilogram every 3 weeks in patients with advanced melanoma, including a cohort of patients who had received prior treatment with the immune checkpoint inhibitor ipilimumab and those who had not. Tumor responses were assessed every 12 weeks. A total of 135 patients with advanced melanoma were treated. Common adverse events attributed to treatment were fatigue, rash, pruritus, and diarrhea; most of the adverse events were low grade. The confirmed response rate across all dose cohorts, evaluated by central radiologic review according to the RECIST 1.1, was 38% (95% confidence interval [CI], 25 to 44), with the highest confirmed response rate observed in the cohort that received 10 mg per kilogram every 2 weeks (52%; 95% CI, 38 to 66). The response rate did not differ significantly between patients who had received prior ipilimumab treatment and those who had not (confirmed response rate, 38% [95% CI, 23 to 55] and 37% [95% CI, 26 to 49], respectively). Responses were durable in the majority of patients (median follow-up, 11 months among patients who had a response); 81% of the patients who had a response (42 of 52) were still receiving treatment at the time of analysis in March 2013. The overall median progression-free survival among the 135 patients was longer than 7 months. These data indicate that high rates of durable responses are achieved with pembrolizumab in patients with advanced melanoma irrespective of any prior treatment with an immune checkpoint inhibitor. Furthermore, the toxicity profile was manageable with the majority grade of the toxicities grade 1 or 2 [53].

4.1.2 Completed Clinical Trials

Three clinical studies have been conducted to evaluate the efficacy of pembrolizumab monotherapy in the treatment of 1L and 2L NSCLC: Keynote-001, Keynote-010, and Keynote-024.

Keynote-001

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

In Keynote-001, a total of 550 advanced 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 objective response rate was 19.4% (18.0% in the 394 previously treated subjects and 24.8% in the 101 previously untreated subjects). The response rate was similar regardless of dose, schedule, and histologic analysis. Current or former smokers had a response rate 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 (tumor proportion score ≥50%) was selected as the cutoff point defining PD-L1 high. In a validation set of 313 subjects, the response rate was 45.2% in the 73 subjects with a tumor proportion score of at least 50%, including 43.9% in previously treated subjects and 50.0% in previously untreated subjects, values that numerically exceeded the response rate in the training group [58].

Pembrolizumab has been generally well-tolerated. The most common treatment related AEs were fatigue (19.4%), pruritus (10.7%), and decreased appetite (10.5%). Adverse events of Grade 3 or higher were reported in 47 of 495 subjects (9.5%). The only treatment-related AE of an inflammatory or immune-mediated nature that occurred in more than 2% of subjects were infusion-related reactions (in 15 subjects [3.0%]), hypothyroidism (in 34 subjects [6.9%]), and pneumonitis (in 18 subjects [3.6%]). One infusion reaction led to treatment discontinuation. All the subjects with hypothyroidism were successfully treated with medical therapy [59].

Keynote-010

Keynote-010 was a randomized, adaptively designed Phase II/III 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.

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 subjects more likely to benefit from pembrolizumab and resulted in favorable HRs in OS compared to docetaxel.

In previously treated subjects with NSCLC with PD-L1 TPS≥1% and disease progression following platinum-containing chemotherapy, pembrolizumab provided a statistically significant and clinically meaningful OS benefit compared to standard docetaxel chemotherapy [60].

Keynote-024

Keynote-024 was a multicenter, international, randomized, open-label, controlled trial of intravenous pembrolizumab monotherapy versus the choice of multiple standard of care 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 (hazard ratio [HR] 0.50; 95% CI: 0.37, 0.68; p<0.001) and OS (HR 0.60; 95% confidence interval [CI]: 0.41, 0.89; p=0.005) compared with SOC chemotherapy, inclusive of pemetrexed maintenance for subjects with non-squamous tumors.

In addition, pembrolizumab was associated with a higher ORR, including a higher CR rate, as well as a longer duration of response as compared to SOC.

Pembrolizumab was better tolerated than chemotherapy and adverse events were manageable. 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 [61].

4.1.3 Information on Other Trial-Related Therapy

Platinum doublets are the standard of care for the treatment of patients with good performance status (ECOG 0 or 1), advanced or metastatic, previously untreated NSCLC and in whom EGFR or ALK-directed therapy is not indicated. Platinum doublets include a platinum compound in combination with gemcitabine, pemetrexed, docetaxel, or bevacizumab [54]. These combinations have demonstrated overall survival gain, improved quality of life, and control of disease-related symptoms compared to single agent regimens.

Multiple Phase III studies have demonstrated similar efficacy for carboplatin plus paclitaxel compared to other platinum doublets, including ECOG 1594 [62]. This is especially significant given that treatment options are limited for squamous histologies.

Further gains in overall survival have been achieved with the administration of pemetrexed maintenance. A Phase III, double-blind study of maintenance pemetrexed plus best supportive care (BSC) versus placebo plus BSC was conducted in subjects with NSCLC whose disease had not progressed following 4 cycles of cisplatin + pemetrexed induction. Subjects were randomized 2:1 to pemetrexed + BSC or placebo + BSC, which were continued until disease progression or toxicity. The median OS for subjects in the intent-to-treat (ITT) group was 13.4 months for subjects receiving pemetrexed and 10.6 months for those receiving placebo (hazard ratio [HR] of 0.79 [95 percent CI: 0.65, 0.95, p=0.012]). Median OS was 15.5 months versus 10.3 months for subjects with non-squamous NSCLC receiving pemetrexed or placebo, respectively (HR of 0.70 [95 percent CI: 0.56, 0.88]). The median OS in subjects with squamous cell NSCLC receiving pemetrexed was 9.9 months versus 10.8 months for those receiving placebo (HR of 1.07 [95 percent CI: 0.77, 1.50]) [62]. These findings have established pemetrexed maintenance following completion of 4 cycles of a platinum doublet induction as a safe and efficacious regimen in patients with advanced or metastatic non-squamous NSCLC.

Given the above, Keynote 042 will allow carboplatin AUC 5 or 6 in combination with either paclitaxel 200 mg/m^2 or pemetrexed 500 mg/m^2 dosed Q3W for a maximum of 6 cycles as a control, chemotherapy option. Each chemotherapy regimen will also allow optional pemetrexed maintenance in patients with non-squamous histologies.

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

Lung cancer had the highest incidence of malignancies globally in 2008 with more than 1.6 million cases. Mortality from lung cancer in 2008 was similar with over 1.4 million deaths from lung cancer globally [63]. 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, multi-modality 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 chemotherapies as single agents or in combination have served as the mainstay of treatment for decades with platinum-containing doublets and maintenance strategies conferring the greatest advances in overall survival gains.

Platinum-based combination chemotherapy prolongs survival, improves quality-of-life, and controls disease-related symptoms. Platinum chemotherapy, thus, is the backbone treatment for initial (first line) treatment of patients not candidates for treatment with tyrosine kinase inhibitors (TKIs). Approved therapies for previously untreated, advanced/metastatic NSCLC subjects in whom EGFR or ALK-directed therapy is not indicted include paclitaxel, gemcitabine, docetaxel, pemetrexed, and bevacizumab, all in combination with platinum-based chemotherapy. While ECOG 1594 demonstrated that the four platinum-doublets tested (cisplatin combined with either paclitaxel, gemcitabine, or docetaxel, and carboplatin and paclitaxel) have equivalent activity in the first-line setting [62], neither pemetrexed nor bevacizumab is appropriate for patients with squamous histology [57] [64] [65].

Recently, targeted therapies for specific tumor genetic alterations have resulted in higher response rates in specific subpopulations of NSCLC patients. Examples include inhibitors against the epidermal growth factor receptor (EGFR) family and the anaplastic lymphoma kinase (ALK). Because of the highly significant demonstration of clinical benefit in these molecularly defined sub-populations, ESMO and NCCN guidelines indicate that first-line treatment with an approved TKI should be prescribed to patients with tumors bearing an activating (sensitizing) epidermal growth factor receptor (EGFR) mutation because of significantly higher response rate (RR), longer PFS, and better quality of life (QoL) (ESMO) when compared with first-line chemotherapy [54]. Recently, a third EGFR inhibitor, afatinib, was approved for the treatment of EGFR inhibitor (TKI) naïve patients with advanced or metastatic NSCLC who bear EGFR-activating mutations on the basis of a significantly improved PFS and acceptable safety, as compared to a SOC platinum doublet of cisplatin + pemetrexed. The composite of data demonstrated a favorable benefit-risk ratio and thus contributes to the arsenal of options for NSCLC patients who harbor EGFR-activating mutations.

Furthermore, recent retrospective analyses indicate that continuation of TKI treatment beyond RECIST-defined progression is associated with a significantly improved overall survival as compared to subjects who were switched to cytotoxic chemotherapies at the time of RECIST-defined PD [66]. The ongoing single arm, Phase II ASPIRATION trial (NCT01310036) aims to prospectively determine if continuation of erlotinib beyond RECIST-defined progression in Asian subjects with EGFR mutations confers clinical benefit. To our knowledge, no randomized studies comparing treatment beyond progression to the traditional paradigm in which cytotoxic chemotherapy is initiated at the time of progression have been performed. Despite these definitive data, the NCCN guidelines recommend that EGFR inhibitors be continued despite PD in asymptomatic patients who harbor EGFR sensitizing mutations, further underscoring the potential to slow the rate of progression and ultimately provide clinical benefit in a patient population with limited therapeutic options in the 2L and beyond.

Patients with NSCLC harboring an anaplastic lymphoma kinase (ALK) translocation should be considered for crizotinib (Xalkori) for the treatment of *ALK*-translocated, previously treated NSCLC.

Despite the development of these targeted therapies, most patients relapse and die from their lung cancer; therefore, advanced and metastatic NSCLC remain a major unmet medical need.

Patients who harbor EGFR sensitizing mutations and/or ALK translocations will be excluded from this study. Significant preclinical and clinical data indicate that activation of these respective pathways fundamentally alter the natural history of tumors that bear these mutations as compared to tumors that do not, which ultimately affect sensitivity to standard of care chemotherapies including pemetrexed in the case of ALK translocations [67]. In addition, EGFR sensitizing mutations confer significant prognostic implications as illustrated by the improved PFS to the SOC platinum doublet, carboplatin and paclitaxel, and overall survival in the EGFR sensitizing mutation population [68]. These mutations also potentially alter PD-L1 expression, likely due to yet undefined interactions between the PD-1/PD-L1/2,

EGFR, and EML4/ALK pathways [69]. These observations indicate that tumors that bear EGFR sensitizing mutations or ALK translocations may be fundamentally different from tumors that do not bear these mutations and may have a different safety and efficacy profile with pembrolizumab as compared to tumors that do not bear these mutations. Given that little data exist regarding the safety and/or efficacy implications of pembrolizumab on these tumors, tumors that bear these mutations will be excluded from this study.

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

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

4.2.1.1 Benefit Risk

In Keynote-001, pembrolizumab continued to provide long-term OS benefit for PD-L1–positive treatment-naive and previously treated NSCLC subjects. As of September 18, 2015, median follow-up duration was 23.1 months. Median OS was 22.1 months (17.1-27.2) for treatment-naive subjects and 10.6 months (8.6-13.3) for previously treated subjects. Eighteen month OS rates were 58.2% and 37.0% respectively; 24-month rates were 44.5% and 31.3%. Pembrolizumab continued to have a manageable safety profile, with no unexpected toxicities observed in long-term follow-up. Of 555 enrolled subjects, 386 (70.2%) experienced ≥1 treatment-related AE, including 66 (12.0%) who experienced ≥1 treatment-related AE of Grade 3-5 severity. Treatment-related AEs led to death in 2 (0.4%) subjects (1 case each of interstitial lung disease and cardiopulmonary arrest) and treatment discontinuation in 29 (5.3%) subjects. Immune-mediated AEs of any grade and grade 3-5 severity occurred in 89 (16.2%) and 22 (4.0%) subjects, respectively and led to treatment discontinuation in 16 (2.9%) subjects. Treatment-related AEs of an inflammatory or immune-mediated nature that occurred in more than 2% of subjects were hypothyroidism (in 44 subjects [8.0%]), pneumonitis (in 22 subjects [4.0%]), and infusion reactions (in 15 subjects [2.7%]). The efficacy results in this study in conjunction with the favorable safety profile demonstrate an overall positive benefit risk assessment.

In addition to Keynote-001 (1L, 2L), Keynote-010 (2L), and Keynote-024 (1L), the ongoing Keynote-042 (IL) study will assess the benefit of pembrolizumab in a previously untreated, advanced NSCLC population who tumors express PD-L1≥50%, PD-L1≥20%, and ≥1%.

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

4.2.2 Rationale for Dose Selection/Regimen/Modification

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

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

In the 8 randomized dose comparison trials, a total of 2262 subjects 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 trials (KN001 B2, KN001 D, KN002, KN010, and KN021) compared 2 mg/kg Q3W vs 10 mg/kg Q3W, and 3 trials (KN001 B3, KN001 F2, and KN006) compared 10 mg/kg Q3W vs 10 mg/kg Q2W. All these trials demonstrated flat dose- and exposure-response relationships across the doses studied, representing an approximate 5 to 7.5-fold difference in exposure. Responses to the dose of 2 mg/kg (or 200 mg fixed dose) Q3W were similar to responses to the highest doses studied. Subsequently, flat dose/exposure-response relationships were 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 interacts with immune cells and does not act via direct binding to cancer cells.

Additionally, pharmacology data clearly show target saturation at 200 mg Q3W. First, PK data from KN001, evaluating target-mediated drug disposition, 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 for pembrolizumab, which characterized the influence of body weight and other subject covariates on exposure, has shown that fixed dosing provides control of PK variability similar to that with weight-based dosing, with considerable overlap in the distribution of exposures from the 200 mg Q3W fixed dose and the 2 mg/kg Q3W dose. Supported by these PK characteristics, and given that a fixed dose has advantages of less dosing complexity and reduced potential for dosing errors, the 200 mg Q3W fixed dose was selected for evaluation across all pembrolizumab protocols.

4.2.3 Rationale for Endpoints

4.2.3.1 Efficacy Endpoints

Primary: Overall survival is a standard assessment of clinical benefit in subjects with advanced and metastatic NSCLC.

Secondary: Progression free survival and ORR are acceptable measures of clinical benefit for a randomized Phase III 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, they are endorsed regulatory endpoints for 1L NSCLC trials with recent FDA and EMA approvals including the EGFR inhibitors, afatinib, and erlotinib. PFS and ORR will be assessed per RECIST 1.1 by central independent radiologists' review that will be blinded to the treatment assignment to minimize any bias in the response assessments.

4.2.3.2 Planned Exploratory Biomarker Research

Additional biomarker research to identify factors important for pembrolizumab therapy may also be pursued. For example, tumor and blood samples (including serum and plasma) from this study may undergo proteomic, genomic, metabolomic and transcriptional analyses. Additional research may evaluate factors important for predicting responsiveness or resistance to pembrolizumab therapy and other immunologic targets.

Assays may include but are not be limited to:

Immunohistochemistry

PD-L1 expression in tumor tissue will be characterized by immunohistochemistry to explore the relationship between tumor PD-L1 expression and response to treatment with pembrolizumab. Other exploratory biomarkers (e.g., PD-1 expression, markers of T-cell phenotype) may also be evaluated.

Transcriptional Analyses

Messenger RNA (mRNA) expression profiling in archival material (biopsy specimens, peripheral blood) will be completed to assess expression of approximately 700 genes and attempt to define a gene set critical for clinical response to pembrolizumab. The hypothesis to be tested is that pembrolizumab induces responses in tumors that reflect an inflamed/ immune phenotype based on gene expression signatures capturing PD-L1 and interferon-gamma transcriptional programs. Global profiling will also be pursued. Expression of individual genes related to the immune system may also be evaluated such as immune signatures and critical cytokines (e.g., IL-10). microRNA profiling may also be pursued in serum samples.

Proteomic Analysis

In addition to expression on the tumor tissue, PD-L1 can be shed from tumor and released into the blood. Enzyme-linked immunoassay can measure PD-L1 in serum and correlate this expression with response to pembrolizumab therapy, as well as levels of PD-L1 IHC or protein in the tumor. Blood would be a less invasive compartment compared to tumor from which to measure PD-L1 protein biomarker. In addition to this specific protein biomarker, both tissue and blood derivatives can be subjected to proteomic profiling studies using a variety of platforms that could include but are not limited to immunoassay, Liquid Chromatography/Mass Spectrometry. This approach could identify novel protein biomarker that could aid in patient selection for pembrolizumab therapy.

Gene Analyses

The application of new technologies, such as next generation sequencing, has provided scientists the opportunity to define certain tumor types at the genetic level as being 'hypermutated' or can detect the presence of specific T-cell clones within the tumor microenvironment or in the peripheral blood. There is a potential that the hypermutated state and/or increased T-cell clonality may correlate with response to pembrolizumab therapy, and/or that the converse, 'hypomutated' state or lack of dominant T-cell clones may correlate with non-response.

In addition, understanding genetic determinants of drug response is an important endeavor during medical research. 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 adverse events, the data might inform optimal use of therapies in the patient population.

4.2.3.3 Future Biomedical Research

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

Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol (as part of the main trial) and will only be conducted on specimens from appropriately consented subjects. The objective of collecting specimens for Future Biomedical Research is to explore and identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments. For instance, exploratory pharmacogenetic (PGt) studies may be performed if significant Pharmacokinetic/Pharmacodynamic (PK/PD) relationships are observed or adverse events are identified. Genomic markers of disease may also be investigated. Such retrospective pharmacogenetic studies will be conducted with appropriate biostatistical design and analysis and compared to PK/PD results or clinical outcomes. Any significant PGt relationships to outcome would require validation in future clinical trials. The overarching goal is to use such information to develop safer, more effective drugs/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 sub-trial are presented in Section 12.2 - Collection and Management of Specimens for Future Biomedical Research. Additional informati onal material for institutional review boards/ethics committees (IRBs/ERCs) and investigational site staff is provided in Section 12.3.

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

Male/female subjects with NSCLC who do not have an EGFR sensitizing mutation and are ALK translocation negative, whose tumors demonstrate PD-L1 expression as determined by a central laboratory, who have received no systemic anti-cancer therapy for their advanced or metastatic NSCLC, and are at least 18 years of age will be enrolled in this trial.

5.1.2 Subject Inclusion Criteria

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

1. Have measurable disease based on RECIST 1.1 as determined by the site.

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

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

4. Have not received prior systemic chemotherapy treatment for their advanced/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 advanced or metastatic disease.

5. Have a performance status of 0 or 1 on the Eastern Cooperative Oncology Group (ECOG) Performance Status.

6. Have adequate organ function as indicated by the following laboratory values in Table 1.

Table 1 Adequate Organ Function Lab Values

System	Laboratory Value[a]
Hematological	
Absolute neutrophil count (ANC)	≥1,500/mcL
Platelets	≥100,000/mcL
Hemoglobin	≥9 g/dL or ≥5.6 mmol/L
Renal	
Serum creatinine OR calculated creatinine clearance (CrCl)[b] (GFR can also be used in place of creatinine or CrCl)	≤1.5 × upper limit of normal (ULN) **OR** ≥50 mL/min for subjects with creatinine levels >1.5 × institutional ULN
Hepatic	
Serum total bilirubin	≤ULN
AST (SGOT) and ALT (SGPT)	≤2.5 × ULN **OR** ≤5 × ULN for patients with liver metastases
Endocrine	
Thyroid stimulating hormone (TSH)	Within normal limits. Note: If TSH is not within normal limits at baseline, the subject may still be eligible if T3 and free T4 are within the normal limits
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT)	≤1.5 × ULN unless the subject is receiving anticoagulant therapy
Activated Partial Thromboplastin Time (aPTT)	≤1.5 × ULN unless the subject is receiving anticoagulant therapy

[a] All screening laboratory tests (local or central) must be reviewed by the investigator or qualified designee and acceptable prior to randomization.
[b] 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)

7. Have no history of prior malignancy, with the exception of basal cell carcinoma of the skin, superficial bladder cancer, squamous cell carcinoma of the skin, or in situ cervical cancer, or have undergone potentially curative therapy with no evidence of that disease recurrence for 5 years since initiation of that therapy.

8. Have provided formalin-fixed tumor tissue sample from a biopsy of a tumor lesion either at the time of or after the diagnosis of advanced or metastatic disease has been made AND from a site not previously irradiated to assess for PD-L1 status.

   Note: Biopsies obtained PRIOR to the administration of any systemic therapy administered for the treatment of a subject's tumor (such as adjuvant therapy) will not permitted for analysis. The tissue sample must be received by the central vendor prior to randomization. Fine needle aspirates are not acceptable. Core needle or excisional biopsies or resected tissue is required.

9. Have a histologically or cytologically confirmed diagnosis of advanced or metastatic NSCLC and not have an EGFR sensitizing (activating) mutation or an ALK translocation.

   Note: EGFR sensitizing mutations are those mutations that are amenable to treatment with TKIs including erlotinib, gefitinib, or afatinib. Investigators must be able to produce the source documentation of the EGFR mutation and ALK translocation in all subjects with non-squamous 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 central laboratory designated by the Sponsor for such testing. Subjects with non-squamous histologies will not be randomized until EGFR mutation status and/or ALK translocation status is available in source documentation at the site.

10. Have a PD-L1 positive (TPS≥1%) tumor as determined by IHC at a central laboratory.

    Note: Only PD-L1 positive (TPS≥1%) subjects will be randomized. If the tumor specimen is not evaluable for PD-L1 expression by the central laboratory, the subject is not eligible to participate in the study.

11. Female subjects must have a negative urine or serum pregnancy test at screening (within 72 hours of first dose of study medication) if of childbearing potential or be of non-child bearing potential. If the urine test is strong or cannot be confirmed as negative, a serum pregnancy test will be required. The serum pregnancy test must be negative for the subject to be eligible. Non-childbearing potential is defined as (by other than medical reasons):

    a. ≥45 years of age and has not had menses for greater than 1 year,

    b. Amenorrheic for <2 years without a hysterectomy and oophorectomy and an FSH value in the postmenopausal range upon pretrial (screening) evaluation,

    c. Whose status is post hysterectomy, oophorectomy, or tubal ligation. Documented hysterectomy or oophorectomy must be confirmed with medical records of the actual procedure or confirmed by an ultrasound. Tubal ligation must be confirmed with medical records of the actual procedure otherwise the subject must be willing to use two adequate barrier methods throughout the study, starting with the screening visit through 120 days after the last dose of study therapy. Please see Section 5.7.2 for a list of acceptable birth control methods. Information must be captured appropriately within the site's source documents.

12. If of childbearing potential, female subjects must be willing to use two adequate barrier methods or a barrier method plus a hormonal method throughout the study, starting with the screening visit (Visit 1) through 120 days after the last dose of pembrolizumab is received and through 180 days after last dose of chemotherapeutic agents as specified in the protocol. Such methods of contraception, or true abstinence from heterosexual activity, when this is in line with the preferred and usual lifestyle of the subject, are required (periodic abstinence, e.g., calendar, ovulation, symptothermal, post-ovulation methods and withdrawal are not acceptable methods of contraception). Please see Section 5.7.2 for a list of acceptable birth control methods.

13. Male subjects with a female partner(s) of child-bearing potential must agree to use two adequate barrier methods or a barrier method plus a hormonal method throughout the trial starting with the screening visit (Visit 1) through 120 days after the last dose of pembrolizumab is received and through 180 days after the last dose of chemotherapeutic agents as specified in the protocol. Such methods of contraception, or true abstinence from heterosexual activity, when this is in line with the preferred and usual lifestyle of the subject, are required (periodic abstinence, e.g., calendar, ovulation, symptothermal, post-ovulation methods and withdrawal are not acceptable methods of contraception). Males with pregnant partners must agree to use a condom; no additional method of contraception is required for the pregnant partner. Please see Section 5.7.2 for a list of acceptable birth control methods.

14. Have voluntarily agreed to participate by giving written informed consent/assent for the trial. The subject may also provide consent/assent for Future Biomedical Research. However, the subject may participate in the main trial without participating in Future Biomedical Research.

5.1.3 Subject Exclusion Criteria

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

1. Has an EGFR sensitizing mutation and/or ALK translocation.

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

2. Is currently participating and receiving study therapy or has participated in a study of an investigational agent and received study therapy or used an investigational device within 4 weeks of the first dose of trial treatment.

3. Tumor specimen is not evaluable for PD-L1 expression by the central laboratory. If an additional tumor specimen is submitted AND evaluable for PD-L1 expression, the subject will be eligible to participate if PD-L1 expression is assessed as positive (TPS≥1%) by the central laboratory.

4. Subjects with squamous histology who received carboplatin in combination with paclitaxel in the adjuvant setting.

5. Is receiving systemic steroid therapy ≤3 days prior to the first dose of trial treatment or receiving any other form of immunosuppressive medication.

   Notes:

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

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

   c. Equivalent hydrocortisone doses are also permitted if administered as a replacement therapy.

6. The subject's NSCLC can be treated with curative intent with either surgical resection and/or chemoradiation.

7. Is expected to require any other form of systemic or localized antineoplastic therapy while on trial (including maintenance therapy with another agent for NSCLC, radiation therapy, and/or surgical resection).

8. Has received any prior systemic cytotoxic chemotherapy, biological therapy OR had major surgery within 3 weeks of the first dose of trial treatment; received lung radiation therapy of >30 Gy within 6 months of the first dose of trial treatment.

9. Has received prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways).

10. Has known central nervous system metastases and/or carcinomatous meningitis.

    Note: Subjects with previously treated brain metastases may participate provided they are clinically stable (neurologically asymptomatic) and have no evidence of new or enlarging brain metastasis by imaging at least 4 weeks after treatment of the brain metastases (e.g., surgery, RT) and are off steroids for at least 3 days prior to the first dose of study medication.

11. Has active autoimmune disease that has required systemic treatment in past 2 years (i.e., with use of disease modifying agents, corticosteroids or immunosuppressive drugs).

    Note: Replacement therapy (i.e., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment. Subjects that require inhaled corticosteroids would not be excluded from the study. Subjects with vitiligo or resolved childhood asthma/atopy would not be excluded from the study. Subjects that require local steroid injections would not be excluded from the study.

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

13. Has interstitial lung disease OR has had a history of pneumonitis that has required oral or IV steroids.

14. Has received or will receive a live vaccine within 30 days prior to the first administration of study medication. Seasonal flu vaccines that do not contain live vaccine are permitted.

15. Has an active infection requiring intravenous systemic therapy.

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

    Note: HIV testing is required at screening as indicated in Section 6.0 – Trial Flow Chart.

17. Has known active Hepatitis B or C. Subjects with a positive HBsAg result would be excluded. Active Hepatitis C is defined by a known positive Hep C Ab result and known quantitative HCV RNA results greater than the lower limits of detection of the assay.

    Note: Hepatitis B and Hepatitis C testing is required at screening as indicated in Section 6.0 – Trial Flow Chart.

18. 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.

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

20. 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).

21. 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 180 days after the last dose of SOC chemotherapy.

5.2 Trial Treatment(s)

The treatment(s) to be used in this trial are outlined below in Table 2.

Table 2 Trial Treatment

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period
Pembrolizumab	200 mg	Q3W	IV	Day 1 of each 21-day cycle
Paclitaxel	200 mg/m^2	Q3W	IV	Day 1 of each 21-day cycle
Carboplatin	AUC 5 or 6	Q3W	IV	Day 1 of each 21-day cycle
Pemetrexed	500 mg/m^2	Q3W	IV	Day 1 of each 21-day cycle and as maintenance in subjects with non-squamous histologies

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

All supplies indicated in Table 2 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 will be responsible for recording the lot number, manufacturer and expiry date of any locally purchased 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 trial treatments in accordance with the protocol and any applicable laws and regulations.

5.2.1 Dose Selection/Modification

5.2.1.1 Dose Selection (Preparation)

The rationale for selection of doses to be used in this trial is provided in Section 4.0 – Background & Rationale.

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

Carboplatin, paclitaxel, and pemetrexed will be prepared and administered as per the approved product label.

5.2.1.2 Dose Modification

Paclitaxel/Carboplatin and Optional Pemetrexed Chemotherapy Regimen

Refer to approved product labels for subjects receiving this regimen.

Pemetrexed/Carboplatin and Optional Pemetrexed Chemotherapy Regimen

Refer to approved product labels for subjects receiving this regimen.

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 with pembrolizumab if that is appropriate at their next scheduled appointment or when toxicity has improved as described in Table 3 below.

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

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

General instructions:

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

Immune-related AEs	Toxicity grade or conditions (CTCAEv4.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor subjects for signs and symptoms of pneumonitis • Evaluate subjects with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment • Add prophylactic antibiotics for opportunistic infections
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor subjects for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus). • Subjects with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. • 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		

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

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

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

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

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

5.2.2 Timing of Dose Administration

Trial treatment may be administered up to 3 days after randomization for Cycle 1 Day 1 due to administrative reasons unless the subject requires pemetrexed pre-medications. For these subjects, the required pre-medications should be administered as close to randomization as possible. After Cycle 1, there is a 3-day window for all trial treatment.

The specific time of pembrolizumab administration (e.g., time of the week for first administration; time of the day for each administration) should take into consideration 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.

Carboplatin: Carboplatin AUC 5 or 6 will be administered as an IV infusion over 30-60 minutes on Day 1 of every 3-week cycle following paclitaxel or pemetrexed infusions (or per local standard practice).

Pemetrexed: Pemetrexed 500 mg/m^2 will be administered as an IV infusion over 10 minutes every 3 weeks and should precede infusion with carboplatin (or per local standard practice). All patients should be pre-medicated with steroids as per approved label and local standard practices. In addition, all subjects assigned to pemetrexed must take a folic acid preparation or multivitamin with folic acid containing between 350 to 1000 mcg daily. At least 5 daily doses of folic acid must be taken during the 7-day period preceding the first dose of pemetrexed and dosing should continue during the full course of therapy and for 21 days after the last dose of pemetrexed.

Subjects must also receive one intramuscular injection of vitamin B12 1000 mcg during the week preceding the first dose of pemetrexed and every 3 cycles thereafter. Subsequent vitamin B12 injections may be given the same day as pemetrexed.

Initiation of the folic acid and vitamin B12 should occur as close to randomization as possible. Pemetrexed will be administered on Cycle 1 Day 1 and every 21 days thereafter.

Paclitaxel: Paclitaxel 200 mg/m^2 will be administered as an IV infusion over 3 hours (or per local standard practice) on Day 1 of every 3-week cycle and should precede infusion with carboplatin.

All subjects receiving the above chemotherapy(s) should be pre-medicated with oral or injectable steroids according to the approved product label and/or standard practice. Additional pre-medications should be administered as per standard practice.

For additional details, refer to approved product labels for details regarding dose calculation, reconstitution, preparation of the infusion fluid, and administration for each of the standard of care chemotherapies.

5.2.3 Trial Blinding/Masking

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

Imaging data for the primary analysis will be centrally reviewed by independent radiologist(s) without knowledge of subject treatment assignment. The subject-level PD-L1 biomarker results (TPS results) will be masked in the database to the study team at the Sponsor including clinical, statistical, statistical programming, and data management person. Access to the PD-L1 subject-level biomarker results (TPS results) will be limited to an unblinded Sponsor clinical scientist, unblinded data management analyst, unblinded Sponsor statistician, and unblinded Sponsor statistical programmer who will be responsible for data review to ensure validity of results but who will have no other responsibilities associated with the study.

5.3 Randomization or 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 and SOC, respectively. The investigator's choice of SOC doublet will be documented prior to randomization in IVRS/IWRS.

5.4 Stratification

Randomization will be stratified according to the following factors:

1. Geography: East Asia vs. non-East Asia
2. ECOG PS: 0 vs. 1
3. Histology: Squamous vs. non-squamous
4. PD-L1 Expression: TPS ≥50% vs. TPS 1-49%

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

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

Palliative and supportive care is permitted during the course of the trial for underlying medical conditions and management of symptoms. Surgery for tumor control or symptom management is not permitted during the study. Palliative radiotherapy is permitted to a single lesion if considered medically necessary by the treating physician as long as the lesion is NOT a RECIST 1.1 defined target lesion and is NOT administered for tumor control. 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. The specifics of the radiation treatment, including the location, will be recorded.

All concomitant medications received within 30 days before the first dose of trial treatment through the Safety Follow-up Visit should be recorded. After the Safety Follow-up Visit, record all medications taken for SAEs and ECIs as defined in Section 7.2.

5.5.2 Prohibited Concomitant Medications and/or Treatments

Subjects are prohibited from receiving the following therapies during the Screening, Treatment, and Second Course Phases of this trial.

- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab
- Surgery for symptom management or tumor control
- Radiation therapy to measurable disease

- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, seasonal flu (that contain a live virus), H1N1 flu, rabies, BCG, and typhoid vaccine.
- Glucocorticoids for any purpose other than to modulate symptoms from an adverse event, serious adverse event, event of clinical interest, for use as a pre-medication for chemotherapeutic agents specified in the protocol, or for use as a pre-medication in subjects with a known history of an IV contrast allergy administered as part of CT radiography. Replacement doses of steroids (for example, prednisone 5-7.5 mg daily) are permitted while on study.
- For subjects assigned to the control arm, concomitant meds should be prohibited as per local standard of care practices and/or the respective package insert details.

Subjects who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the trial.

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

The Exclusion Criteria describes other medications that 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

Pembrolizumab

Pembrolizumab subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator including but not limited to the items outlined below.

- Diarrhea: Subjects should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus). In symptomatic subjects, infectious etiologies should be ruled out, and if symptoms are persistent and/or severe, endoscopic evaluation should be considered. All subjects who experience diarrhea should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.

  For additional guidance and/or treatment recommendation, please refer to the separate Events of Clinical Interest (ECI) and Immune-related Adverse Events (irAE) Guidance Document. For guidelines for continuing treatment with pembrolizumab, see Section 5.2.

- Nausea/Vomiting: Administration of prophylaxis for nausea and vomiting should be administered per institutional guidelines and local standard practices for the standard of care chemotherapies offered for the control arm. For MK 3475, the therapy is considered to be of low to moderate emetogenic potential. Consideration for chemo-induced nausea and vomiting prophylaxis should be given in subsequent cycles of the administration according to standard institutional practice. Subjects should be strongly encouraged to maintain liberal oral fluid intake.

- Anemia: Transfusions and/or erythropoietin may be utilized as clinically indicated for the treatment of anemia, but should be clearly noted as concomitant medications. Consider a potential immunologic etiology.

- Neutropenia: Prophylactic use of colony-stimulating factors including Granulocyte Colony-Stimulating Factor (G-CSF), pegylated G-CSF or Granulocyte Macrophage Colony-Stimulating Factor (GM CSF) is not allowed in this trial. Therapeutic use of G-CSF is allowed in subjects with Grade 3-4 febrile neutropenia. Consider a potential immunologic etiology.

- Thrombocytopenia: Transfusion of platelets may be used if clinically indicated. ITP should be ruled out before initiation of platelet transfusion.

- Anti-infectives: Subjects with a documented infectious complication should receive oral or IV antibiotics or other anti-infective agents as considered appropriate by the treating Investigator for a given infectious condition, according to standard institutional practice.

- Events of Clinical Interest (ECI) with a Potential Immunologic Etiology: Please see the separate guidance document in the administrative binder regarding identification, evaluation, and management of adverse experiences of a potential immunologic etiology. Depending on the type and severity of an ECI, oral or intravenous treatment with a corticosteroid should be considered, in addition to appropriate symptomatic treatment of a given condition.

5.6.2 Overview of Guidelines for Managing Suspected Pneumonitis from Pembrolizumab

The treatment of symptomatic subjects with pneumonitis differs from asymptomatic subjects with pneumonitis. Subjects with symptomatic pneumonitis should immediately stop receiving pembrolizumab and have an evaluation, with consideration of further work up including a bronchoscopy, cultures, and pulmonary function tests, to assess severity and to rule out other causes such as infection.

Please consult the ECI and irAE Guidance document in the Administrative Binder for this study for a more in depth discussion of pneumonitis.

5.6.3 Guidelines for Infusion Reactions

Pembrolizumab

Acute infusion reactions (which can include cytokine release syndrome, angioedema, or anaphylaxis) are different from allergic/hypersensitive reactions, although some of the manifestations are common to both AEs. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Signs/symptoms may include: allergic reaction/hypersensitivity (including drug fever); arthralgia (joint pain); bronchospasm; cough; dizziness; dyspnea (shortness of breath); fatigue (asthenia, lethargy, malaise); headache; hypertension; hypotension; myalgia (muscle pain); nausea; pruritus/itching; rash/desquamation; rigors/chills; sweating (diaphoresis); tachycardia; tumor pain (onset or exacerbation of tumor pain due to treatment); urticaria (hives, welts, wheals); vomiting.

Table 4 shows treatment guidelines for subjects who experience an infusion reaction associated with administration of pembrolizumab:

Table 4 Pembrolizumab Infusion Reaction Treatment Guidelines

NCI CTCAE Grade	Treatment	Pre-medication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤24 hours	**Stop Infusion** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be pre-medicated for the next scheduled dose. Subjects who develop Grade 2 toxicity despite adequate pre-medication should be permanently discontinued from further trial treatment administration.	Subject may be pre-medicated 1.5 hours ± 30 minutes prior to infusion of pembrolizumab with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine) Acetaminophen 500-1000 mg po (or equivalent dose of analgesic)
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief	**Stop Infusion** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS	No subsequent dosing

NCI CTCAE Grade	Treatment	Pre-medication at Subsequent Dosing
interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. Subject is permanently discontinued from further trial treatment administration.	
Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events (CTCAE) v4.0 at http://ctep.cancer.gov.		

5.7 Diet/Activity/Other Considerations

5.7.1 Diet

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

5.7.2 Contraception

Pembrolizumab may have adverse effects on a fetus in utero. Furthermore, it is not known if pembrolizumab has transient adverse effects on the composition of sperm. Chemotherapy can cause fetal harm if administered to pregnant women. Therefore, non-pregnant, non-breastfeeding women may be enrolled if they are considered highly unlikely to conceive. Highly unlikely to conceive is defined as (1) surgically sterilized or (2) postmenopausal (a woman who is ≥45 years of age and has not had menses for greater than 1 year will be considered postmenopausal) or (3) amenorrheic for <2 years without a hysterectomy and oophorectomy and with a documented FSH value in the postmenopausal range or (4) not heterosexually active for the duration of the study or (5) heterosexually active and willing to use two methods of birth control (which is also recommended for the female partners of male subjects). The two birth control methods can be either two barrier methods or a barrier method plus a hormonal method to prevent pregnancy. Subjects should start using birth control from study Visit 1 throughout the study period up to 120 days after the last dose of pembrolizumab and up to 180 days after last dose of chemotherapeutic agents as specified in the protocol.

The following are considered adequate barrier methods of contraception: diaphragm, condom (by the partner), copper intrauterine device, sponge, or spermicide, as per local regulations and guidelines. Appropriate hormonal contraceptives will include any registered and marketed contraceptive agent that contains an estrogen and/or a progestational agent (including oral, subcutaneous, intrauterine, or intramuscular agents). 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 they must adhere to the contraception requirement (described above) for the duration of the study and during the follow-up period defined in Section 7.2.2 – Reporting of Pregnancy and Lactation to the Sponsor. If there is any question that a subject will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

Such methods of contraception, or true abstinence from heterosexual activity, when this is in line with the preferred and usual lifestyle of the subject, are required (periodic abstinence, e.g., calendar, ovulation, symptothermal, post-ovulation methods and withdrawal are not acceptable methods of contraception). Males with pregnant partners must agree to use a condom; no additional method of contraception is required for the pregnant partner.

5.7.3 Use in Pregnancy

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

5.7.4 Use in Nursing Women

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

5.8 Subject Withdrawal/Discontinuation Criteria

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

In this trial, a subject may discontinue from treatment but continue to participate in the regularly scheduled activities, as long as the subject does not withdraw consent. Once a subject has discontinued treatment, even though he/she continues to be monitored in the trial, he/she may be allowed to begin treatment again if deemed medically appropriate.

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

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

5.8.1 Discontinuation from Treatment

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

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

- Documented progression

  Note: If a subject has confirmed progression of disease by modified RECIST 1.1, it is recommended that the subject be discontinued from trial unless, in the investigator's opinion, the subject is deriving benefit from treatment. Clinically stable subjects as defined below may continue to receive trial therapy after consultation with the Sponsor. Subjects exhibiting toxicity from trial therapy as outlined in Sections 5.2.1.2 and 7.2 may NOT continue to receive trial therapy. Regardless of clinical benefit, the maximum number of treatments a subject may receive is 35. If a subject has unconfirmed progression of disease and is clinically stable, it is at the discretion of the investigator to continue treating the subject with the assigned treatment per protocol until progression of disease is confirmed at least 28 days from the date of the scan suggesting progression of disease. If progression is not confirmed on the subsequent scan, the subject should continue to receive study therapy and radiographic scans obtained to monitor for disease status every 9 weeks as defined in Section 7.1.2.6.

  Clinical Stability is defined as:

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

  2. No decline in ECOG performance status.

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

- Unacceptable adverse experiences as described in Section 5.2.1.2.

- Two years of uninterrupted delivery of pembrolizumab every 3 weeks and no documented progression of disease**, or 35 administrations of study medication, whichever is later**

- Intercurrent illness that prevents further administration of treatment
- Investigator's decision to withdraw the subject
- The subject has a confirmed strong serum pregnancy test
- Noncompliance with trial treatment or procedure requirements
- The subject is lost to follow-up
- Administrative reasons

If a pembrolizumab treated subject attains an investigator-assessed CR according to modified RECIST 1.1, has been treated for at least 6 months with pembrolizumab, and has at least two 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 pembrolizumab after attaining a CR (or have experienced a PR or SD after 35 administrations of pembrolizumab) and then experience radiographic disease progression according to modified RECIST 1.1 will be eligible for re-treatment with pembrolizumab in the Second Course Phase at the discretion of the investigator as described in Section 7.1.5.5. Subjects randomized to pembrolizumab 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.

Chemotherapy may be discontinued when a subject has received the maximum number of cycles as outlined in the protocol.

If subjects discontinue treatment for any reason other than progression or pregnancy, the same assessments and frequency of assessments should be obtained as outlined in the Observation Phase of the study.

After the end of treatment, each subject will be followed for a minimum of 30 days for adverse event monitoring (SAEs and ECI 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). Subjects will have post-treatment follow-up for disease status with pembrolizumab.

5.8.2 Pembrolizumab End of Treatment Follow-up

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

5.9 Subject Replacement Strategy

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

5.10 Beginning and End of the Trial

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

At the time the OS analysis has been triggered, all subjects will have the opportunity to complete at least 24 months of treatment (or discontinue from treatment for progression or other reasons). The last visit of the last subject will be considered the end of the trial.

5.11 Clinical Criteria for Early Trial Termination

Early trial termination will be the result of the criteria specified below:

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

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

Further recruitment in the trial or at (a) particular trial site(s) may be stopped due to insufficient compliance with the protocol, GCP and/or other applicable regulatory requirements, procedure-related problems or the number of discontinuations for administrative reasons is too high.

6.0 TRIAL FLOW CHART

6.1 Pembrolizumab Arm: Treatment and Follow-up Phase

	Screening (Visit 1)	Treatment Cycles[1]													End of Treatment Phase		Observation Phase[2] (pre-PD)	Follow-up Phase[3]			Survival Follow-up[4]
																		1	2	Every 3 Months after Visit 2	Approx. Every 2 Months
Treatment Cycle/ Scheduled Time	-42 to -1	1	2	3	4	5	6	7	8	9	10	11	12	13 and beyond	Discontinuation Visit[5]	Safety Follow-up Visit[6]	Observation Visits[7]	Follow-up Visit 1[8]	Follow-up Visit 2[8]	Follow-up Visit 3 and beyond[8]	Survival Follow-up Visit 1 and beyond
Scheduling Window (Days):[9]		±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	At study drug discontinuation ±3	30 days from last dose ±3	±3 days	±7 days	±7 days	±7 days	±14 days
Administrative Procedures																					
Informed Consent	X																				
Informed Consent for Future Biomedical Research (optional)	X																				
Inclusion/Exclusion Criteria	X																				
Subject ID 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	X				
NSCLC Disease Details and Prior Treatment	X																				
Subsequent Antineoplastic Therapy Status															X	X	X	X	X	X	X
Survival Status[4,10]		←----------																		----------→	X

	Screening (Visit 1)	Treatment Cycles[1]													End of Treatment Phase		Observation Phase[2] (pre-PD)	Follow-up Phase[3]			Survival Follow-up[4]
																		1	2	Every 3 Months after Visit 2	Approx. Every 2 Months
Treatment Cycle/ Scheduled Time	-42 to -1	1	2	3	4	5	6	7	8	9	10	11	12	13 and beyond	Discontinuation Visit[5]	Safety Follow-up Visit[6]	Observation Visits[7]	Follow-up Visit 1[8]	Follow-up Visit 2[8]	Follow-up Visit 3 and beyond[8]	Survival Follow-up Visit 1 and beyond
Scheduling Window (Days):[9]		±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	At study drug discontinuation ±3	30 days from last dose ±3	±3 days	±7 days	±7 days	±7 days	±14 days
Clinical Procedures/Assessments																					
Review Adverse Events[11]		X	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	X		
Vital Signs and Weight[12]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
12-Lead ECG	X																				
ECOG Performance Status	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Central Laboratory Procedures/Assessments																					
Blood for Future Biomedical Research (Optional)[13]		X																			
Blood for Serum Biomarkers[14]		X																			
Blood for Plasma Biomarkers[14]		X																			
Correlative Studies Blood Collection (DNA and RNA)[15]		X	X	X											X						
Blood for Genetics[16]		X																			
Study Drug Administration																					
Pembrolizumab[17]		X	X	X	X	X	X	X	X	X	X	X	X	X[17]							

	Screening (Visit 1)	Treatment Cycles[1]												End of Treatment Phase		Observation Phase[2] (pre-PD)	Follow-up Phase[3]			Survival Follow-up[4]
																	1	2	Every 3 Months after Visit 2	Approx. Every 2 Months
Treatment Cycle/ Scheduled Time	-42 to -1	1	2	3	4	5	6	7	8	9	10	11	12	13 and beyond	Discontinuation Visit[5]	Safety Follow-up Visit[6]	Observation Visits[7]	Follow-up Visit 1[8]	Follow-up Visit 2[8]	Follow-up Visit 3 and beyond[8]	Survival Follow-up Visit 1 and beyond
Scheduling Window (Days):[9]		±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	At study drug discontinuation ±3	30 days from last dose ±3	±3 days	±7 days	±7 days	±7 days	±14 days
Local Laboratory Procedures/Assessments																					
Pregnancy Test - Urine or Serum β-HCG[18]	X[18]																				
PT/INR and aPTT[19]	X[20]																				
CBC with Differential[21,22]	X[20]		X	X	X	X	X	X	X	X	X		X[21]		X	X	X[23]				
Comprehensive Chemistry Panel[21, 22]	X[20]		X	X	X	X	X	X	X	X	X		X[21]		X	X	X[23]				
Urinalysis[22,24]	X[20]					X				X				X[25]	X	X	X[23]				
T3, FT4 and TSH[22,25]	X[20]		X		X		X		X		X		X[25]		X	X	X[23]				
ALK Translocation Testing[26]	X																				
EGFR Mutation Testing[26]	X																				
HBsAG[27]	X																				
Anti HCV[27]	X																				
Anti HIV[27]	X																				
Efficacy Measurements																					
Tumor Imaging[28]	X				X			X			X			X	X[28]	X[28]	X[28]	X[8]	X[10]	X[10]	
Tumor Biopsies/Archival Tissue Collection																					
Tumor Tissue Collection for PD-L1 Expression[29]	X																				

1	In general, assessments/procedures are to be performed on Day 1 and prior to the first dose of trial treatment for each cycle unless otherwise specified. Treatment cycles are 3 weeks (21 days). 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 9 weeks ± 7 days from the date of randomization regardless of any treatment delays.
2	The Observation Phase is for any subject that discontinued study treatment for reasons other than pregnancy or PD (e.g., toxicity). Pembrolizumab subjects remain in the Observation Phase until the time of PD, pregnancy, or the start of a new antineoplastic therapy.
3	Subjects who stop pembrolizumab after 35 trial treatments and have achieved PR and/or SD will move to the Follow-up Phase of the study. Follow-up visit 1 should take place 3 months after the last dose of trial treatment. Follow-up visit 2 should take place 6 months after last dose of trial treatment and additional Follow-up visits should take place every 3 months thereafter. Subjects who experience disease progression (and do not continue into the Second Course Phase) or start a new antineoplastic therapy will move directly into Survival Follow-up.
4	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 approximately every 2 months to assess for survival status. Post-study treatments and the subject's response to them will also be collected. 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 and its respective entry into the database (excluding subjects who have a death event previously recorded).
5	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. Imaging assessments should continue as per the interval stated in the protocol: every 9 weeks for the first 15 cycles and then every 12 weeks thereafter. Additional imaging at the discontinuation visit is not required provided that imaging assessments have been performed per schedule.
6	The mandatory Safety Follow-up Visit for all subjects should be conducted approximately 30 days after the last dose of trial treatment or before the initiation of new antineoplastic treatment, whichever comes first. Subjects with an AE of Grade >1 will be further followed until the resolution of the AE to Grade 0-1 or until beginning of a new antineoplastic therapy, whichever occurs first. Subjects who are eligible for treatment with pembrolizumab during the Second Course Phase may have up to two Safety Follow-up Visits, one after the Treatment Phase and the second after the Second Course Phase. If the Discontinuation Visit occurs approximately 30 days (± 3 days) from last dose trial treatment the same procedures do not need to be repeated for the Safety Follow-up Visit. Imaging assessments should continue as per the interval stated in the protocol: every 9 weeks for the first 15 cycles 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	Observation visits should begin 4 weeks (28 days ± 7 days) from the Safety Follow-up Visit and follow a Q3W (21 days ± 3 days) schedule thereafter. Tumor imaging for the Observation Visits should be maintained Q9W by following the same calendar day schedule that was initiated during Treatment Cycles. For subjects who have received at least 15 treatment cycles of pembrolizumab, the frequency of tumor imaging may be reduced to every 12 weeks (84 ± 7 days) during the Observation Visits.
8	For subject convenience, all Follow-up assessments may occur during the same visit as the imaging studies are obtained. Subjects with an AE of Grade >1 will be further followed until the resolution of the AE to Grade 0-1 or until beginning of a new antineoplastic therapy, whichever occurs first.
9	In general, the window for each visit is ±3 days unless otherwise specified.
10	Tumor imaging is not needed for subjects who start another anti-cancer treatment regimen.
11	Once a subject discontinues study treatment, report all SAEs (related and unrelated to trial treatment), ECIs, and irAEs occurring within 90 days following cessation of treatment or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier. After this time, report only SAEs and ECIs that are considered related to trial treatment.
12	Vital signs to include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at screening only.
13	Informed consent for Future Biomedical Research (FBR) samples must be obtained before the DNA sample is drawn. DNA sample for analysis should be obtained pre-dose, on Cycle 1 (or with the next scheduled blood draw), as the last sample drawn, on allocated subjects only, or at a later date as soon as the informed consent is obtained. This sample should only be taken once from each subject. See Section 12.2 for guidance regarding the collection and management of specimens for FBR.
14	Samples for plasma and serum biomarkers should be obtained pre-dose Cycle 1.
15	Samples for correlative studies should be obtained pre-dose at Cycles 1, 2, 3, and at the time of study drug discontinuation.
16	Blood for genetics sample will be collected to explore host genetics and to identify genetic predictors that may have a role in therapeutic response to pembrolizumab. This sample should be drawn for planned, exploratory genetic analysis of DNA unless there is either a documented law or regulation prohibiting collection, or unless the IRB/IEC does not approve of the collection.
17	Pembrolizumab can be administered for up to 35 treatments.

18 For women of reproductive potential, a urine pregnancy test will be performed within 72 hours prior to first dose of trial treatment. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test, performed by the local study site laboratory, will be required. Pregnancy tests (serum and/or urine tests) should be repeated if required by local guidelines.
19 Coagulation factors (PT/INR and aPTT) should be monitored closely throughout the trial for any subject receiving anticoagulant therapy.
20 Laboratory tests for screening are to be performed within 10 days prior to the first dose of trial treatment.
21 CBC with differentials and chemistry will be performed every cycle up to Cycle 10, then every other cycle thereafter.
22 After Cycle 1, lab samples can be collected up to 7 days prior to the scheduled time point. Laboratory results must be known and acceptable prior to dosing.
23 During the Observation Phase, these laboratory assessments should be obtained every 12 weeks.
24 Perform every 4 cycles.
25 Thyroid function tests will be performed by a central laboratory only if the local laboratory is unable to perform this service. Thyroid function tests will be performed every other cycle.
26 Site must be able to provide documentation of the subject's tumor EGFR mutation and/or ALK translocation mutation status if clinically indicated. If the site is unable to provide this source documentation, or site level testing, then the Sponsor will offer this molecular testing of the tumor.
27 The need for additional testing due to positive test results will be at the discretion of the Investigator.
28 Sponsor will collect radiological assessments for analysis by a central vendor. The initial tumor imaging will be performed within 30 days prior to the date of randomization. Scans performed as part of routine clinical management are acceptable for use as the screening scan if they are of diagnostic quality and performed within 30 days prior to the date of randomization. On study imaging will be performed every 9 weeks (63 ± 7 days) after the date of randomization or more frequently if clinically indicated and submitted for central radiology review. The timing for imaging studies should follow calendar days and should not be adjusted for delays in cycle starts or extension of pembrolizumab cycle frequencies. The same imaging technique should be used in a subject throughout the trial. After week 45 tumor imaging, tumor imaging should be performed every 12 weeks (84 ± 7 days). CT scan of the chest, abdomen and pelvis is required for the baseline assessment. After the first documentation of progression (if the subject is clinically stable) or response per modified RECIST 1.1 repeat imaging for confirmation may be performed. Confirmatory imaging may be performed as early as 28 days later; alternately, the scan performed at the next scheduled time point (e.g., every 63 ±7 days) may be used as confirmation. Details are provided in the Image Acquisition Guidelines.
29 Tumor tissue for biomarker analysis from a biopsy of a tumor lesion not previously irradiated must be provided. Only biopsies obtained AFTER the diagnosis of metastatic disease will be evaluated for PD-L1 expression. Any leftover tumor tissue will be stored for future research if the subject signs the optional FBR consent. If a tumor biopsy was obtained from a target lesion during eligibility assessment, it is preferred to obtain a new baseline scan. Biopsy of lesions on study should be limited to non-target lesions or new lesions if their pathologic etiology is ambiguous.

6.2 Standard of Care Arm: Treatment and Follow-up Phase

	Screening (Visit 1)	**Treatment Cycles[1]**													**End of Treatment Phase**		**Observation Phase[2] (pre-PD)**	**Survival Follow-up[3]** **Approx. Every 2 Months**
Treatment Cycle/ Scheduled Time	-42 to -1	1	2	3	4	5	6	7	8	9	10	11	12	13 and beyond	Discontinuation Visit[4]	Safety Follow-up Visit[5]	Observation Visits[6,7]	Survival Follow-up Visit 1 and beyond
Scheduling Window (Days):[8]		±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	At study drug discontinuation ±3	30 days from last dose ±3	±3 days	±14 days
Administrative Procedures																		
Informed Consent	X																	
Informed Consent for Future Biomedical Research (optional)	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	X	
NSCLC Disease Details and Prior Treatment	X																	
Subsequent Antineoplastic Therapy Status															X	X	X	X
Survival Status[3,9]		<--->																X

	Screening (Visit 1)	Treatment Cycles[1]													End of Treatment Phase		Observation Phase[2] (pre-PD)	Survival Follow-up[3]
Treatment Cycle/ Scheduled Time	-42 to -1	1	2	3	4	5	6	7	8	9	10	11	12	13 and beyond	Discontinuation Visit[4]	Safety Follow-up Visit[5]	Observation Visits[6,7]	Survival Follow-up Visit 1 and beyond
Scheduling Window (Days):[8]		±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	At study drug discontinuation ±3	30 days from last dose ±3	±3 days	±14 days
Clinical Procedures/Assessments																		
Review Adverse Events[10]		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[11]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
12-Lead ECG	X																	
ECOG Performance Status	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Central Laboratory Procedures/Assessments																		
Blood for Future Biomedical Research (Optional)[12]		X																
Blood for Serum Biomarkers[13]		X																
Blood for Plasma Biomarkers[13]		X																
Correlative Studies Blood (DNA and RNA)[14]		X	X	X											X			
Blood for Genetics[15]		X																
Study Drug Administration																		
Paclitaxel/Carboplatin[16]		X	X	X	X[16]	X[16]	X[16]											

	Screening (Visit 1)	Treatment Cycles[1]													End of Treatment Phase		Observation Phase[2] (pre-PD)	Survival Follow-up[3]
																		Approx. Every 2 Months
Treatment Cycle/ Scheduled Time	-42 to -1	1	2	3	4	5	6	7	8	9	10	11	12	13 and beyond	Discontinuation Visit[4]	Safety Follow-up Visit[5]	Observation Visits[6,7]	Survival Follow-up Visit 1 and beyond
Scheduling Window (Days):[8]		±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	At study drug discontinuation ±3	30 days from last dose ±3	±3 days	±14 days
Pemetrexed/Carboplatin[16]		X	X	X	X[16]	X[16]	X[16]											
Pemetrexed						X	X	X	X	X	X	X	X	X				
Local Laboratory Procedures/Assessments																		
Pregnancy Test - Urine or Serum β-HCG[17]	X[17]																	
PT/INR and aPTT[18]	X[19]																	
CBC with Differential[20,21]	X[19]		X	X	X	X	X	X	X	X	X		X[20]		X	X	X[22]	
Comprehensive Chemistry Panel[20, 21]	X[19]		X	X	X	X	X	X	X	X	X		X[20]		X	X	X[22]	
Urinalysis[21, 23]	X[19]					X				X				X[23]	X	X	X[22]	
T3, FT4 and TSH[21, 24]	X[19]		X		X		X		X		X		X[24]		X	X	X[22]	
ALK Translocation Testing[25]	X																	
EGFR Mutation Testing[25]	X																	
HBsAG[26]	X																	
Anti HCV[26]	X																	
Anti HIV[26]	X																	
Efficacy Measurements																		
Tumor Imaging[27]	X				X			X			X			X[27]	X[27]	X[27]	X[9,27]	
Tumor Biopsies/Archival Tissue Collection																		
Tumor Tissue Collection for PD-L1 Expression[28]	X																	

1 In general, assessments/procedures are to be performed on Day 1 and prior to the first dose of trial treatment for each cycle unless otherwise specified. Treatment cycles are 3 weeks (21 days). If treatment cycles are increased all procedures except imaging will be completed according to the cycle number and not weeks on treatment; imaging will be performed every 9 weeks ± 7 days from the date of randomization regardless of any treatment delays.
2 The Observation Phase is for any subject that discontinued study treatment for reasons other than pregnancy or PD.
3 Subjects who experiences disease progression or start a new antineoplastic therapy will move into Survival Follow-up and should be contacted by telephone approximately every 2 months to assess for survival status and the start of any new antineoplastic therapy. The subject's response to new treatments will also be collected. 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 and its respective entry into the database (excluding subjects who have a death event previously recorded).
4 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. Imaging assessments should continue as per the interval stated in the protocol: every 9 weeks for the first 15 cycles and then every 12 weeks thereafter. Additional imaging at the Discontinuation Visit is not required provided that imaging assessments have been performed per schedule.
5 The mandatory Safety Follow-up Visit for all subjects should be conducted approximately 30 days after the last dose of trial treatment or before the initiation of new antineoplastic treatment, whichever comes first. Subjects with an AE of Grade >1 will be further followed until the resolution of the AE to Grade 0-1 or until beginning of a new antineoplastic therapy, whichever occurs first. Subjects who are eligible for treatment with pembrolizumab during the Second Course Phase may have up to two Safety Follow-up Visits, one after the Treatment Phase and the second after the Second Course Phase. If the Discontinuation Visit occurs approximately 30 days ± 3 days from last dose of trial treatment the same procedures do not need to be repeated for the Safety Follow-up Visit. Imaging assessments should continue as per the interval stated in the protocol: every 9 weeks for the first 15 cycles 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.
6 Observation visits should begin 4 weeks (28 days ± 7 days) from the Safety Follow-up Visit and follow a Q3W (21 days ± 3 days) schedule thereafter. All assessments and procedures should be obtained per the Observation Visit schedule until the subject experiences PD. Tumor imaging for the Observation Visits should be maintained Q9W by following the same calendar day schedule that was initiated during Treatment Cycles. Subjects who have received total of 15 cycles (SOC plus pemetrexed maintenance) may reduce the frequency of tumor imaging to every 12 weeks (84 ± 7 days) during the Observation Visits.
7 Subjects with an AE of Grade >1 will be further followed until the resolution of the AE to Grade 0-1 or until beginning of a new antineoplastic therapy, whichever occurs first.
8 In general, the window for each visit is ±3 days unless otherwise specified.
9 Tumor imaging is not needed for subjects who start another anti-cancer treatment regimen.
10 Once a subject discontinues study treatment, report all SAEs (related and unrelated to trial treatment), ECIs, and irAEs occurring within 90 days following cessation of treatment or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier. After this time, report only SAEs and ECIs that are considered related to trial treatment.
11 Vital signs to include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at screening only.
12 Informed consent for Future Biomedical Research (FBR) samples must be obtained before the DNA sample is drawn. DNA sample for analysis should be obtained pre-dose, on Cycle 1 (or with the next scheduled blood draw), as the last sample drawn, on allocated subjects only, or at a later date as soon as the informed consent is obtained. This sample should only be taken once from each subject. See Section 12.2 for guidance regarding the collection and management of specimens for FBR.
13 Samples for plasma and serum biomarkers should be obtained pre-dose Cycle 1.
14 Samples for correlative studies should be obtained pre-dose at Cycles 1, 2, 3, and at the time of study drug discontinuation.
15 Blood for genetics sample will be collected to explore host genetics and to identify genetic predictors that may have a role in therapeutic response to pembrolizumab. This sample should be drawn for planned, exploratory genetic analysis of DNA unless there is either a documented law or regulation prohibiting collection, or unless the IRB/IEC does not approve of the collection.
16 SOC will be administered for 4 - 6 cycles.
17 For women of reproductive potential, a urine pregnancy test will be performed within 72 hours prior to first dose of trial treatment. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test, performed by the local study site laboratory, will be required. Pregnancy tests (serum and/or urine tests) should be repeated if required by local guidelines.
18 Coagulation factors (PT/INR and aPTT) should be monitored closely throughout the trial for any subject receiving anticoagulant therapy.
19 Laboratory tests for screening are to be performed within 10 days prior to the first dose of trial treatment.
20 CBC with differentials and chemistry will be performed every cycle up to Cycle 10, then every other cycle thereafter.

21 After Cycle 1, lab samples can be collected up to 7 days prior to the scheduled time point. Laboratory results must be known and acceptable prior to dosing.
22 During the Observation Phase laboratory assessments should be obtained every 12 weeks.
23 Perform every 4 cycles.
24 Thyroid function tests will be performed by a central laboratory only if the local laboratory is unable to perform this service. Thyroid function tests should be performed every other cycle.
25 Site must be able to provide documentation of the subject's tumor EGFR mutation and/or ALK translocation mutation status if clinically indicated. If the site is unable to provide this source documentation, or site level testing, then the Sponsor will offer this molecular testing of the tumor.
26 The need for additional testing due to positive test results will be at the discretion of the Investigator.
27 Sponsor will collect radiological assessments for analysis by a central vendor. The initial tumor imaging will be performed within 30 days prior to the date of randomization. Scans performed as part of routine clinical management are acceptable for use as the screening scan if they are of diagnostic quality and performed within 30 days prior to the first dose of trial treatment. On study imaging will be performed every 9 weeks (63 ± 7 days) after the date of randomization or more frequently if clinically indicated and submitted for central radiology review. Imaging studies should follow calendar days and should not be adjusted for delays in cycle starts or extension. The same imaging technique should be used in a subject throughout the trial. After week 45 tumor imaging, tumor imaging should be performed every 12 weeks (84 ± 7 days). CT scan of the chest, abdomen and pelvis is required for the baseline assessment. After the first documentation of progression (if the subject is clinically stable) or response per modified RECIST 1.1 repeat imaging for confirmation may be performed. Confirmatory imaging may be performed as early as 28 days later; alternately, the scan performed at the next scheduled time point (e.g., every 63 ±7 days) may be used as confirmation. Details are provided in the Image Acquisition Guidelines.
28 Tumor tissue for biomarker analysis from a biopsy of a tumor lesion not previously irradiated must be provided. Only biopsies obtained AFTER the diagnosis of metastatic disease will be evaluated for PD-L1 expression. Any leftover tumor tissue will be stored for future research if the subject signs the optional FBR consent. If a tumor biopsy was obtained from a target lesion during eligibility assessment, it is preferred to obtain a new baseline scan. Biopsy of lesions on study should be limited to non-target lesions or new lesions if their pathologic etiology is ambiguous.

6.3 Second Course Treatment and Follow-up Phase for Pembrolizumab Arm

	Second Course Treatment Cycles[1]													End of Second Course Treatment		Follow-up[2]			Survival Follow-up[3]
																1	2	Every 3 Months after Visit 2	Approx. Every 2 Months
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[4]	Follow-up Visit 1	Follow-up Visit 2	Follow-up Visit 3 and Beyond	Survival Follow-up Visit 1 and Beyond
Scheduling Window (Days):[5]	±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[3,6]	←--→																		X
Study Drug Administration																			
Pembrolizumab[7]	X	X	X	X	X	X	X	X	X	X	X	X	X						
Clinical Procedures/Assessments																			
Review Adverse Events[6]	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[8]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
ECOG Performance Status	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Laboratory Procedures/Assessments: Analysis Performed by Local Laboratory[11]																			
Pregnancy Test - Urine or Serum β-HCG[9]	X																		
PT/INR and aPTT[10]	X[11]																		

	Second Course Treatment Cycles[1]													End of Second Course Treatment		Follow-up[2]			Survival Follow-up[3]
																1	2	Every 3 Months after Visit 2	Approx. Every 2 Months
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[4]	Follow-up Visit 1	Follow-up Visit 2	Follow-up Visit 3 and Beyond	Survival Follow-up Visit 1 and Beyond
Scheduling Window (Days):[5]	±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
CBC with Differential[12, 14]	X[11]	X	X	X	X	X	X	X	X	X		X[12]		X	X[13]	X[13]	X[13]		
Comprehensive Chemistry Panel[12,14]	X[11]	X	X	X	X	X	X	X	X	X		X[12]		X	X[13]	X[13]	X[13]		
Urinalysis[15]	X[11]				X				X				X[15]	X	X				
T3, FT4 and TSH[14, 16]	X[11]		X		X		X		X		X		X[16]	X	X[13]	X[13]	X[13]		
Efficacy Measurements																			
Tumor Imaging[17,18]	X			X			X			X			X[18]	X	X[17]	X	X	X	

1	In general, assessments/procedures are to be performed on Day 1 and prior to the first dose of trial treatment for each cycle unless otherwise specified. Treatment cycles are 3 weeks (21 days). 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 9 weeks (63 ± 7 days) from the date of randomization regardless of any treatment delays.
2	Subjects who discontinue trial treatment for a reason other than disease progression will move into the Follow-up Phase and should be assessed every 9 weeks (63 ± 7 days) by radiologic imaging to monitor disease status. Follow-up Visit 1 should be scheduled 3 months after the last dose of trial treatment. Follow-up Visit 2 should occur 6 months after the last dose of trial treatment. After Follow-up Visit 2 subjects only need to be assessed every 9 weeks (63 ± 7 days) by radiologic imaging to monitor disease status, development of drug-related SAEs and ECIs, and initiation of new antineoplastic therapy. Unless otherwise noted in the flow chart, every effort should be made to collect subject information until the start of new antineoplastic therapy, disease progression or death, whichever occurs first.
3	Once a subject experiences disease progression or starts a new antineoplastic therapy, the subject moves into the Survival Follow-up Phase and should be contacted by telephone approximately every 2 months to assess for survival status and start of new antineoplastic therapy if applicable. Updated survival status may be requested by the Sponsor at any time during the course of the study. Upon Sponsor notification, all 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 and its respective entry into the database (excluding subjects who have a death event previously recorded).
4	The mandatory Safety Follow-Up Visit should be conducted approximately 30 days after the last dose of trial treatment or before the initiation of a new antineoplastic treatment, whichever comes first. Subjects with an AE of Grade >1 will be further followed until the resolution of the AE to Grade 0-1 or until beginning of a new antineoplastic therapy, whichever occurs first. Subjects who are eligible per the requirements in Section 7.1.5.5 for treatment with pembrolizumab during the Second Course Phase may have up to two Safety Follow-up Visits, one after the Treatment Phase and the second after the Second Course Phase.
5	In general, the window for each visit is ±3 days unless otherwise specified.
6	Record all AEs occurring within 30 days after the last dose of trial treatment. Report all SAEs (related and unrelated to trial treatment), ECIs, and irAEs occurring within 90 days following cessation of treatment or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier. After this time, report only SAEs and ECIs that are considered related to trial treatment.
7	Pembrolizumab can be administered up to 17 trial treatment in Second Course Phase.
8	Vital signs to include temperature, pulse, respiratory rate, blood pressure, and weight.
9	For women of reproductive potential, a urine pregnancy test will be performed within 72 hours prior to the first Second Course dose. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test, performed by the local study site laboratory, will be required. Pregnancy tests (serum and/or urine tests) should be repeated if required by local guidelines.
10	Coagulation factors (PT/INR and aPTT) should be monitored closely throughout the trial for any subject receiving anticoagulant therapy.
11	Laboratory tests for determining eligibility for Second Course Phase are to be performed within 10 days prior to the first dose of pembrolizumab. See Section 7.1.3 for details regarding laboratory tests.
12	CBC with differentials and chemistry will be performed every cycle up to Cycle 10, then every other cycle thereafter.
13	Every effort should be made to collect blood samples at the Safety Follow-up Visit, Follow-up Visit 1, and Follow-up Visit 2 until the start of new antineoplastic therapy, disease progression or death, whichever comes first.
14	After the first dose, lab samples can be collected up to 7 days prior to the scheduled time point. Laboratory results must be known and acceptable prior to dosing. See Section 7.1.3 for details regarding laboratory tests.
15	Perform every 4 cycles.
16	Thyroid function tests will be performed by a central laboratory only if the local laboratory is unable to perform this service. Thyroid function tests should be performed every other cycle.
17	Subjects who discontinue trial treatment due to reasons other than disease progression should continue to be assessed every 9 weeks (63 ± 7 days) by radiologic imaging until the start of a new antineoplastic therapy, documented disease progression, or death, whichever occurs first. If trial treatment is discontinued after Cycle 13, tumor imaging should be performed every 12 weeks (84 days ± 7 days). Continued imaging is not needed for subjects who start another antineoplastic treatment. The same imaging technique should be used in a subject throughout the trial.
18	Sponsor will collect radiological assessments for analysis by a central vendor. If the subject enters the Second Course Phase, Cycle 1 scan may be performed up to 30 days prior to the first dose of trial treatment in the Second Course Phase. Imaging will be performed every 9 weeks (63 ± 7 days) after the first dose of Second Course Phase trial treatment up until Cycle 13 and every 12 weeks (84 ± 7 days) thereafter. The timing of imaging should follow calendar days and should not be adjusted for delays in cycle starts or extension of pembrolizumab cycle frequencies. The same imaging technique should be used in a subject throughout the trial.

7.0 TRIAL PROCEDURES

7.1 Trial Procedures

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

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

7.1.1 Administrative Procedures

7.1.1.1 Informed Consent

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

7.1.1.1.1 General Informed Consent

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

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

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

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

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

7.1.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

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

7.1.1.2 Inclusion/Exclusion Criteria

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

7.1.1.3 Subject Identification Card

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

7.1.1.4 Medical History

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

7.1.1.5 Prior and Concomitant Medications Review

7.1.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the subject within 30 days before the first dose of trial treatment. In addition, record all treatments for a prior cancer other than NSCLC even if taken greater than 30 days prior to first dose. Prior treatments for NSCLC will be recorded separately and not listed as a prior medication.

7.1.1.5.2 Concomitant Medications

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

7.1.1.6 Non-Small Cell Lung Cancer (NSCLC) Disease Details and Treatments

7.1.1.6.1 Disease Details

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

7.1.1.6.2 Prior Treatment

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

7.1.1.6.3 Subsequent Antineoplastic Therapy Status

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

7.1.1.7 Assignment of Screening Number

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

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

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

7.1.1.8 Assignment of Randomization Number

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

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

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

Interruptions from the protocol specified treatment plan for 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.

Administration of trial medication will be witnessed by the investigator and/or trial staff. The total volume of trial treatment infused will be compared to the total volume prepared to determine compliance with each dose administered.

7.1.2 Clinical Procedures/Assessments

7.1.2.1 Adverse Event (AE) Monitoring

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

An immune-related adverse event (irAE) may be defined as an adverse event of unknown etiology, associated with drug exposure and is consistent with an immune phenomenon. Efforts should be made to rule out neoplastic, infectious, metabolic, toxin or other etiologic causes prior to labeling an adverse event immune-related. Immunological, serological and histological (biopsy) data should be used to support the diagnosis of an immune-related toxicity. Following the guidance described in Section 7.2.3.2, certain irAEs should also be reported to the Sponsor as ECIs. (See the separate guidance document in the administrative binder regarding the identification, evaluation, and management of irAEs and ECIs.)

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

7.1.2.2 Physical Exam

7.1.2.2.1 Full Physical Exam

The investigator or qualified designee will perform a complete physical exam during the screening period. Clinically significant abnormal findings should be recorded as medical history. The time points for full physical exam 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 Exam

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

7.1.2.3 Vital Signs

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

7.1.2.4 Lead Electrocardiogram (ECG)

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

7.1.2.5 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status (see Section 12) at screening, prior to the administration of each dose of trial treatment and during the Follow-up period as specified in the Trial Flow Chart. ECOG status must be 0 or 1 at time of first dose of study medication.

7.1.2.6 Tumor Assessments and Imaging

Sponsor will collect radiological assessments for analysis by a central vendor.

The initial tumor imaging will be performed within 30 days of randomization date. Scans performed as part of routine clinical management are acceptable for use as the screening scan if they are of diagnostic quality and performed within 30 days prior to the randomization date. CT scan of the chest, abdomen, and pelvis is required for the baseline assessment.

On-study tumor assessments for subjects randomized to either the pembrolizumab or control arms are to be performed every 9 weeks (63 ± 7 days) or more frequently if clinically indicated, from the date of randomization until radiographic PD has been established. For subjects who continue on therapy beyond week 45, tumor imaging should be performed every 12 weeks (84 ± 7 days). Timing should follow calendar days and should not be adjusted for delays in cycle starts or extension of cycle frequencies.

After the first documentation of response per modified RECIST 1.1, confirmatory scans may be performed as early as 28 days later; alternately, the scan performed at the next scheduled time point (e.g., every 63 ±7 days) may be used as confirmation for response. After the first documentation of progression per modified RECIST 1.1, confirmatory scans may be performed 4 to 6 weeks later (if the subject is clinically stable).

After the first documentation of progression, it is at the discretion of the investigator to keep a clinically stable subject on trial treatment or to stop trial treatment until repeat imaging performed 4-6 weeks later confirms progression.

Clinical Stability is defined as:

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

2. No decline in ECOG performance status.

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

Subjects that are deemed clinically unstable are not required to have repeat imaging for confirmation. If progression is confirmed, it is recommended that the subject be discontinued from trial treatment unless, in the investigator's opinion, the subject is deriving benefit from treatment. Clinically stable subjects as defined above may continue to receive trial therapy after discussion with the Sponsor. Subjects exhibiting toxicity from trial therapy as outlined in Sections 5.2.1 and 7.2 may NOT continue to receive trial therapy. Regardless of clinical benefit, the maximum number of treatments a subject may receive is 35.

If progression is not confirmed, then the subject should resume/continue trial treatment and have their next scan according to the every 9-week (63 ± 7 days) schedule from first dose of study treatment, which would be approximately 9 weeks from the date of the scan that first showed progression. When feasible, subjects should not be discontinued until progression is confirmed.

Subjects who move into the Second Course Phase will continue to have scans performed every 9 weeks (63 ± 7 days) up to Cycle 13 and then every 12 weeks (84 ± 7 days).

The same imaging technique should be used in a subject throughout the trial. Details are provided in the Procedures Manual.

7.1.2.7 Tumor Tissue Collection

Tumor tissue for biomarker analysis from formalin-fixed paraffin embedded tumor tissue sample or newly obtained formalin-fixed biopsy of a tumor lesion not previously irradiated must be provided in the form of a tissue block or unstained slides and received by the central vendor before randomization. Only subjects whose tumors demonstrate positive (TPS ≥1%) PD-L1 expression are eligible for enrollment. A fine needle aspirate or cytologic specimen will not be acceptable. Core needle or excisional biopsies, or resected tissue is required. Newly obtained formalin-fixed specimens are encouraged and highly recommended if the patient's archival sample was obtained ≥ 6 months prior to screening.

If the subject signs the Future Biomedical Research (FBR) consent, any leftover tissue biopsies that would ordinarily be discarded at the end of the main study will be retained for FBR, again providing the 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.

7.1.3 Laboratory Procedures/Assessments

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

7.1.3.1 Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

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

Table 5 Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Blood	Follicle stimulating hormone (FSH)
Hemoglobin	Alkaline phosphatase	Glucose	Serum β-human chorionic gonadotropin (β-hCG)
Platelet count	Alanine aminotransferase (ALT)	Protein	Triiodothyronine (T3 or FT3)
WBC (total and/or differential)	Aspartate aminotransferase (AST)	Specific gravity	Free thyroxine (FT4)
RBC	Carbon dioxide (CO_2 or bicarbonate)[a]	Microscopic exam, if abnormal results are noted	Thyroid stimulating hormone (TSH)
	Calcium		PT (INR)
	Chloride		aPTT
	Creatinine		Blood for FBR (optional)
	Glucose		Blood for genetics
	Magnesium		Blood for correlative studies
	Phosphorus		Blood for biomarkers
	Potassium		HBs AG
	Sodium		Anti HCV
	Total bilirubin		Anti HIV
	Direct bilirubin, if total bilirubin is elevated above the upper limit of normal		
	Total protein		
	Blood urea nitrogen (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.

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

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

7.1.3.2 Pharmacokinetic/Pharmacodynamic Evaluations

Accumulation of robust PK and ADA data has allowed adequate characterization of the clinical pharmacology of pembrolizumab across indications. Therefore, collection of PK and ADA samples is being discontinued for subjects enrolled under Amendment 06. Blood samples for PK and ADA collected prior to Amendment 06 may be stored. Analysis will be performed only if required.

7.1.3.3 Molecular Testing

Site must be able to provide documentation of subject's tumor EGFR mutation and/or ALK translocation status. If the site is unable to provide this source documentation, then the Sponsor will offer this molecular testing of the tumor. Detailed instructions for tissue collection, processing and shipment are provided in the Procedures Manual.

7.1.3.4 Future Biomedical Research

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

- Blood for genomics use
- Leftover tumor tissue

7.1.4 Other Procedures

7.1.4.1 Withdrawal/Discontinuation

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

7.1.4.1.1 Withdrawal From Future Biomedical Research

Subjects may withdraw their consent for Future Biomedical Research and have their specimens and all derivatives destroyed. Subjects may withdraw consent at any time by contacting the principal investigator for the main trial. If medical records for the main trial are still available, the investigator will contact the Sponsor using the designated mailbox PPD, and a form will be provided by the Sponsor to obtain appropriate information to complete specimen withdrawal. Subsequently, the

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

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

7.1.4.2 Blinding/Unblinding

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

7.1.4.3 Calibration of Critical Equipment

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

Critical Equipment for this trial includes:

- Laboratory equipment – as required for inclusion labs and trial assessments
- Imaging equipment – as required for study objectives
- Safety equipment – as required for safety assessments
- Drug administration equipment – as required for storage, preparation and administration of study drugs

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

7.1.5 Visit Requirements

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

7.1.5.1 Screening

Approximately 42 days prior to randomization, potential subjects will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5.1. Screening procedures may be repeated after consultation with the Sponsor.

Written consent must be obtained prior to performing any protocol specific procedure. Results of a test performed prior to the subject signing consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame. Screening procedures are to be completed within 42 days prior to the first dose of trial treatment except for the following:

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

- For women of reproductive potential, a urine pregnancy test will be performed within 72 hours prior to first dose of trial treatment. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test, performed by the local study site laboratory, will be required.

- Tumor imaging must be performed within 30 days prior to the 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 Phase

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

7.1.5.3 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. Imaging assessments should continue as per the interval stated in the protocol: every 9 weeks for the first 15 cycles and then every 12 weeks thereafter. Additional imaging at the discontinuation visit is not required provided that imaging assessments have been performed per schedule.

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 0-1 or until beginning of a new antineoplastic therapy, whichever occurs first.

Subjects who are eligible per the requirements in Section 7.1.5.5 for treatment with pembrolizumab during the Second Course Phase may have up to two Safety Follow-up Visits, one after the Treatment Phase and the second after the Second Course Phase.

Imaging assessments should continue as per the interval stated in the protocol: every 9 weeks for the first 15 cycles 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.

7.1.5.3.3 Observation Visit

Subjects who complete their fixed number of 4 - 6 cycles of SOC or who stop either SOC (including pemetrexed maintenance) or pembrolizumab for reasons other than PD or pregnancy, should move into the Observation Phase of the study and complete the assessments in the Observation Visits schedule as outlined in the study flow chart in Section 6.0. If a subject experiences PD, they automatically move to the Survival Follow-up Phase of the flowchart.

Subjects randomized to pembrolizumab who discontinue therapy due to a PR and/or SD after 35 trial treatments should follow procedures in the End of Treatment Phase and Follow-up Phase of the study. If PD is established during the assessments obtained during the Follow-up Phase of the study, the subject may be eligible for the Second Course Phase.

Laboratory tests including CBC with differentials, thyroid function tests, CMP and urinalysis should be obtained every 3 months during the Observation Visit Phase.

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 trial treatment for a reason other than disease progression should continue to receive all assessments as outlined in the Observation Phase of the study in Section 6.0 until PD by investigator-assessed modified RECIST 1.1 or initiation of a new antineoplastic therapy.

Subjects who are randomized to pembrolizumab and have received the maximum administrations of pembrolizumab indicated above, should be followed as indicated in the Follow-up Phase of the study outlined in Section 6.0.

Follow-up Visit 1 should be scheduled 3 months after the last dose of trial treatment. Assessment for drug-related immune-related adverse events should occur at Follow-up Visit 1. Follow-up Visit 2 should occur 6 months after the last dose of trial treatment. Unless otherwise noted in the flowchart, every effort should be made to collect subject information on the start of new antineoplastic therapy, disease progression, death.

Subjects who are eligible to receive re-treatment with pembrolizumab according to the criteria in Section 7.1.5.5 will move to the Second Course Phase when they experience disease progression

Imaging will be performed every 9 weeks (63 ± 7 days) after the first dose of Second Course Phase trial treatment until Cycle 13 and then every 12 weeks (84 ± 7 days) thereafter. The timing of imaging should follow calendar days and should not be adjusted for delays in cycle starts or extension of pembrolizumab cycle frequencies. The same imaging technique should be used in a subject throughout the trial. Subjects who discontinue trial treatment from the Second Course Phase for a reason other than disease progression will move into the Follow-up Phase and should continue to be assessed every 9 weeks (63 ± 7 days) by radiologic imaging to monitor disease status or every 12 weeks (84 ± 7 days) after Cycle 13. Continued imaging is not needed for subjects who start another anti-cancer treatment regimen.

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 approximately every 2 months to assess for survival status. Survival assessments and its respective entry into the database may be required more frequently around the projected analysis. Post-study treatments and the subject's response to them will also be collected.

7.1.5.5 Second Course Phase

Visit requirements are outlined in Section 6.0 – Trial Flow Chart. Specific procedure-related details are provided above in Section 7.1 – Trial Procedures. Subjects who were randomized to receive pembrolizumab may be eligible to receive up to 17 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 retreatment with pembrolizumab on study.

Subjects will be eligible to receive pembrolizumab in the Second Course Phase of this study if the subject:

- Stopped their initial treatment with pembrolizumab after attaining a confirmed CR according to modified RECIST 1.1, was treated for at least 6 months with pembrolizumab, and received at least two treatments with pembrolizumab beyond the date when the initial CR was declared. A CR by modified RECIST 1.1 means that all index lesions have resolved (none have bidimensional measurements), all non-index lesions have disappeared, and no new lesions have been identified. These findings must be confirmed on subsequent imaging at least 4 weeks later for the call of CR by modified RECIST 1.1 to be appropriate. As such, the subject will have no evidence of metastatic cancer in order for the subject and his/her physician to consider the subject's participation in this Second Course Phase.

- Experienced an investigator-determined confirmed radiographic disease progression according to modified RECIST 1.1 after stopping their initial treatment with pembrolizumab due to achievement of a confirmed CR.

- Have received 35 administrations of pembrolizumab while in SD or better and then experience an investigator-determined confirmed radiographic disease progression according to modified RECIST 1.1.

- Did not receive any anti-cancer treatment since the last dose of pembrolizumab.

- Continues to meet inclusion criteria 3, 5, 6, 11, 12, and 13.

- Does not meet exclusion criteria 3, 5, 9 to 18, and/or 19.

Subjects will be re-treated at the same dose as when they last received pembrolizumab. An objective response or progression of disease assessed by investigator-reviewed modified RECIST 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.

7.1.5.6 Survival Status

To ensure current and complete survival data are available at the time of database locks, updated survival data 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 (DMC) review, interim, and/or final analysis. 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 and its respective entry into the database (excluding subjects who have a previously recorded death event in the collection tool).

7.2 Assessing and Recording Adverse Events

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

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

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

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

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

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

From the time of treatment allocation/randomization through 30 days following cessation of treatment, all adverse events must be reported by the investigator. Such events will be recorded at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in section 7.2.3.1. The investigator will make every attempt to follow all subjects with non-serious adverse events for outcome.

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

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

For purposes of this trial, an overdose will be defined as any dose exceeding the prescribed dose for the SOC chemotherapy by more than 20%. For subjects treated with pembrolizumab an overdose will be defined as any dose exceeding 5 x the protocol-prescribed dose. No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, pembrolizumab or the chemotherapy should be discontinued and the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

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

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

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

7.2.2 Reporting of Pregnancy and Lactation to the Sponsor

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

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

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

7.2.3 Immediate Reporting of Adverse Events to the Sponsor

7.2.3.1 Serious Adverse Events

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

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

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

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

Refer to Table 6 for additional details regarding each of the above criteria.

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

For the time period beginning at treatment allocation/randomization through 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study (reference Section 7.2.3.3 for additional details), whether or not related to the Sponsor's product, must be reported within 24 hours to the Sponsor either by electronic

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

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

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

7.2.3.2 Events of Clinical Interest

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

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

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

Events of clinical interest for this trial include:

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

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

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

3. Additional adverse events:

   A separate guidance document has been provided entitled "Event of Clinical Interest Guidance Document" (previously entitled, "Event of Clinical Interest and Immune-Related Adverse Event Guidance Document"). This document can be found in the administrative binder and provides guidance regarding identification, evaluation, and management of ECIs and irAEs.

   ECIs (both non-serious and serious adverse events) identified in this guidance document from the date of first dose through 90 days following cessation of treatment, or 30 days after the initiation of a new anticancer therapy, whichever is earlier, need to be reported to the Sponsor **within 24 hours** of the event, regardless of attribution to study treatment, consistent with standard SAE reporting guidelines and either by electronic media or paper. Sponsor Contact information can be found in the administrative binder.

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

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 experience to the single agent.

Table 6 Evaluating Adverse Events

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

V4.0 CTCAE Grading	**Grade 1**	**Mild; asymptomatic or mid symptoms; clinical or diagnostic observations only; intervention not indicated.**
	Grade 2	**Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.**
	Grade 3	**Severe or medically significant but not immediately life-threatening; hospitalization or prolongation or hospitalization indicated; disabling; limiting self-care ADL.**
	Grade 4	**Life threatening consequences; urgent intervention indicated.**
	Grade 5	**Death related to AE**
Seriousness	A serious adverse event is any adverse event occurring at any dose or during any use of Sponsor's product that:	
	†**Results in death**; or	
	†**Is life threatening; or** places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred (Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.); or	
	†**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or	
	†**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization 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) **or**	
	Is an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event. 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 test drug	Did the Sponsor's product cause the adverse event? The determination of the likelihood that the Sponsor's product caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the adverse event based upon the available information. **The following components are to be used to assess the relationship between the Sponsor's product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Sponsor's product caused the adverse event (AE):	
	Exposure	Is there evidence that the subject was actually exposed to the Sponsor's product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
	Time Course	Did the AE follow in a reasonable temporal sequence from administration of the Sponsor's product? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors

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

7.2.5 Sponsor Responsibility for Reporting Adverse Events

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

7.3 TRIAL GOVERNANCE AND OVERSIGHT

7.3.1 Scientific Advisory Committee

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

7.3.2 Trial Steering Committee

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

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

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

7.3.3 Executive Oversight Committee

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

7.3.4 Data Monitoring Committee

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

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

A DMC recommendation will be communicated to the EOC as agreed to in the DMC charter.

8.0 STATISTICAL ANALYSIS PLAN

8.1 Statistical Analysis Plan Summary

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

Study Design Overview	A Randomized, Open Label, Phase III Study of Overall Survival Comparing Pembrolizumab versus Platinum Based Chemotherapy in Treatment Naïve Subjects with TPS≥1% Advanced or Metastatic Non-Small Cell Lung Cancer
Treatment Assignment	Subjects will be randomized in a 1:1 ratio to receive pembrolizumab or SOC chemotherapy. Stratification factors are in Section 5.4.
Analysis Populations	Efficacy: Intent to Treat (ITT) subjects with TPS≥50%, TPS≥20%, and TPS≥1% Safety: All Subjects as Treated (ASaT)
Primary Endpoints	1. Overall Survival (OS) in subjects with TPS≥50%, 1L advanced/metastatic NSCLC 2. OS in subjects with TPS≥20%, 1L advanced/metastatic NSCLC 3. OS in subjects with TPS≥1%, 1L advanced/metastatic NSCLC
Statistical Methods for Key Efficacy Analyses	The primary hypotheses will be evaluated by comparing pembrolizumab arm to SOC chemotherapy arm on OS using a stratified Log-rank test. Estimation of the hazard ratio (HR) will be done using a stratified Cox regression model. Event rates over time will be estimated within each treatment group using the Kaplan-Meier method.
Statistical Methods for Key Safety Analyses	The analysis of safety results will follow a tiered approach. There is no Tier I safety endpoint for this trial. Point estimates and 95% confidence intervals (CIs) for between-treatment comparisons via the Miettinen and Nurminen method will be provided for Tier 2 safety endpoints; only point estimates by treatment group will be provided for Tier 3 safety endpoints.
Interim Analyses	Two interim analyses will be performed in this study. Results will be reviewed by an external DMC. Details are provided in Section 8.2.9.
	• Interim Analysis 1 (IA1) 1. Timing: At least 250 deaths observed in 2 arms in the subjects with TPS≥50% AND at least 6 months after last subject is enrolled. [redacted] 2. Purpose: Demonstrate superiority of pembrolizumab in OS • Interim Analysis 2 (IA2) 1. Timing: About 38 months after study start 2. Purpose: Demonstrate superiority of pembrolizumab in OS • Final Analysis (FA) 1. [redacted] 2. Purpose: Demonstrate superiority of pembrolizumab in OS

Multiplicity	The overall Type-I error is strongly controlled at 2.5% (1-sided) for the 3 primary hypotheses (superiority of pembrolizumab in OS in subjects with TPS≥50%, TPS≥20% and TPS≥1%) and 6 secondary hypotheses (superiority of pembrolizumab in PFS in subjects with TPS≥50%, TPS≥20% and TPS≥1%, superiority of pembrolizumab in ORR in subjects with TPS≥50%, TPS≥20% and TPS≥1%). The hypotheses will be tested sequentially at the type I error rate of 2.5% (one-sided) in the following order: 1. Superiority of pembrolizumab in OS in the subjects with TPS≥50% 2. Superiority of pembrolizumab in OS in the subjects with TPS≥20% 3. Superiority of pembrolizumab in OS in the subjects with TPS≥1% 4. Superiority of pembrolizumab in PFS in the subjects with TPS≥50% 5. Superiority of pembrolizumab in PFS in the subjects with TPS≥20% 6. Superiority of pembrolizumab in PFS in the subjects with TPS≥1% 7. Superiority of pembrolizumab in ORR in the subjects with TPS≥50% 8. Superiority of pembrolizumab in ORR in the subjects with TPS≥20% 9. Superiority of pembrolizumab in ORR in the subjects with TPS≥1%. Under this sequential testing strategy, a hypothesis will be tested only if superiority is established for all the preceding ones. The initial alpha allocation is revised to reflect the change of the criteria for the conduct of the FA and the addition of IA2. The reallocation of alpha occurs after IA1, and proper adjustment is made to maintain the control of family-wise type I error rate with the implementation of this change. The type I error actually spent at IA1 will be kept intact and the re-allocation will only be applied to the remaining unspent alpha. No futility boundary will be set as before. Both IA2 and FA will be conducted based on calendar time. Specifically, [redacted] Under the revised alpha allocation, the alpha spending is determined by the Hwang-Shih-DeCani alpha spending function with the gamma parameter -0.9023. With this spending function, the alpha level at IA1 is the same as the actual spent at IA1 (one-sided 1.576%) based on the scale of calendar time fraction 0.729 (i.e., 986/1353). The cumulative alpha (one-sided) spending at the planned time of IA2 and FA becomes 1.94% and 2.5%, regardless of the actual number of deaths observed at the IA2 and FA. The corresponding stopping bounds at IA2 and FA will then be calculated based on the cumulative alpha spent and actual number of deaths observed at each analysis. Testing of the PFS hypotheses will be performed at the same interim analyses and FA. The cumulative alpha spending is determined by the same alpha spending function (on the scale of calendar time) defined above for the OS hypotheses. Statistical significance under multiplicity control can only be established once the OS hypotheses have been established at an interim or the FA. Otherwise, nominal p-values will be reported as a measure of strength of association for the PFS hypotheses. Testing of the ORR hypotheses will be based on the IA1 data. Statistical significance under multiplicity control can only be established once the OS and PFS hypotheses have both been established. Otherwise, nominal p-values will be reported as a measure of strength of association for the ORR hypotheses. If OS and PFS are not statistically significant at IA1, then the ORR at IA1 will be considered without any data update if the step-down criteria allow formal testing based on a later analysis of OS and PFS.

Sample Size and Power	[redacted] the overall sample size for this study is projected to be approximately 1240. The number of randomized subjects with TPS≥50% drives the end of enrollment. [redacted]

8.1.1 Efficacy Analyses

The intention-to-treat (ITT) populations in the subjects with TPS≥50%, TPS≥20% and TPS≥1% will serve as the primary populations for the analyses of efficacy data in this trial. The primary efficacy endpoint is overall survival (OS) (i.e., the time from randomization to death due to any cause). The secondary efficacy endpoints are progression-free survival (PFS) (i.e., time from randomization to documented progressive disease or death due to any cause, whichever occurs first) per RECIST 1.1 based on blinded central independent radiologists' review, and objective response rate (ORR) per RECIST 1.1 based on blinded central independent radiologists' review. An outline of the analysis strategy for key efficacy endpoints is presented in Table 7.

Table 7 Analysis Strategy for Key Efficacy Endpoints

Endpoint (Description, Time Point)	Statistical Method	Analysis Population	Missing Data Approach
Primary			
OS	Testing: Stratified Log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT with TPS≥50%, TPS≥20% and TPS≥1%	Model based
Secondary			
PFS (per blinded central independent radiologists'-assessed RECIST 1.1)	Testing: Stratified Log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT with TPS≥50%, TPS≥20% and TPS≥1%	Model based
ORR (per blinded central independent radiologists'-assessed RECIST 1.1)	Testing: stratified Miettinen and Nurminen method with weights proportional to the stratum size	ITT with TPS≥50%, TPS≥20% and TPS≥1%	Subjects with missing data are considered non-responders

8.1.2 Safety Analyses

The All Subjects as Treated (ASaT) population in the subjects with TPS≥1% will be used for the primary analysis of safety data in this study.

Investigators will be asked to report adverse experiences at every visit on this study (at least every 3 weeks during treatment) using Common Terminology Criteria for Adverse Events, Version 4.0. The attribution to drug, time-of-onset, duration of the event, its resolution, and any concomitant medications administered will be reported. AEs will be analyzed and reported for between arm differences in various parameters, including Events of Clinical Interest outlined in the separate Event of Clinical Interest Guidance Document, all AEs, SAEs, fatal AEs, and laboratory changes. Safety analyses follow a tiered approach and the details are stated in Section 8.2.5.2.

8.1.3 Multiplicity Adjustment

The multiplicity strategy specified in this section will be applied to the ITT populations with TPS≥50%, TPS≥20%, and TPS≥1% for the testing of the OS, PFS, and ORR hypotheses. The overall type I error is strongly controlled at 2.5% (one-sided). The hypotheses will be tested sequentially at the type I error rate of 2.5% (one-sided) in the following order: superiority of pembrolizumab in OS in the subjects with TPS≥50%, superiority of pembrolizumab in OS in the subjects with TPS≥20%, superiority of pembrolizumab in OS in

the subjects with TPS≥1%, superiority of pembrolizumab in PFS in the subjects with TPS≥50%, superiority of pembrolizumab in PFS in the subjects with TPS≥20%, superiority of pembrolizumab in PFS in the subjects with TPS≥1%, superiority of pembrolizumab in ORR in the subjects with TPS≥50%, superiority of pembrolizumab in ORR in the subjects with TPS≥20%, and superiority of pembrolizumab in ORR in the subjects with TPS≥1%. Under this sequential testing strategy, a hypothesis will be tested only if superiority is established for all the preceding ones.

The initial alpha allocation is revised to reflect the change of the criteria for the conduct of the FA and the addition of IA2. The reallocation of alpha occurs after the conduct of IA1, and proper adjustment is made to maintain the control of family-wise type I error rate with the implementation of this change. The type I error actually spent at IA1 will be kept intact and the re-allocation will only be applied to the remaining unspent alpha. No futility boundary will be set as before.

Both IA2 and FA will be conducted based on calendar time [70]. Specifically, [redacted] will occur about 38 months [redacted]. Under the revised alpha allocation, the alpha spending at IA2 and FA is determined by the Hwang-Shih-DeCani alpha spending function with the gamma parameter -0.9023. With this spending function, the alpha level at IA1 is the same as the actual spent at IA1 (one-sided 1.576%), since the information fraction is 0.729 (i.e., 986/1353) on the scale of calendar time. The cumulative alpha (one-sided) spending at the planned time of IA2 and FA becomes 1.94% and 2.5%, regardless of the actual number of deaths observed at the IA2 and FA. The corresponding stopping bounds at IA2 and FA will then be calculated based on the cumulative alpha spent and actual number of deaths observed at each analysis.

If the pembrolizumab arm demonstrates superior OS in the subjects with TPS≥50% at an interim or FA, the OS hypothesis in the subjects with TPS≥20% will be tested based on the same group sequential approach (on the scale of calendar time) so that the cumulative alpha spent up to each interim analysis is at the same level as the alpha spent for testing the OS hypothesis in the subjects with TPS≥50% up to that analysis [71]. Note that, based on the above sequential testing strategy, if the OS superiority is demonstrated at an interim analysis in the subjects with TPS≥50%, the OS superiority in the subjects with TPS≥20% may be demonstrated at a later analysis. If the pembrolizumab arm demonstrates superior OS in the subjects with both TPS≥50% and TPS≥20%, the OS hypothesis in the subjects with TPS≥1% will be tested using the same approach.

Testing of the PFS hypotheses will be performed at the same interim analyses and FA. The cumulative alpha spending is determined by the same alpha spending function (on the scale of calendar time) defined above for the OS hypotheses. The corresponding stopping bounds for PFS at IA2 and FA will then be calculated based on the actual number of deaths observed at each analysis. Statistical significance under multiplicity control can only be established once the OS hypotheses have been established at an interim or the FA. Otherwise, nominal p-values will be reported as a measure of strength of association for the PFS hypotheses.

Testing of the ORR hypotheses will be based on the IA1 data. Statistical significance under multiplicity control can only be established once the OS and PFS hypotheses have both been established. Otherwise, nominal p-values will be reported as a measure of strength of association for the ORR hypotheses. If OS and PFS are not statistically significant at IA1, then the ORR at IA1 will be considered without any data update if the step-down criteria allow formal testing based on a later analysis of OS and PFS.

8.1.4 Power and Sample Size

The study will randomize subjects in a 1:1 ratio into the pembrolizumab arm and the SOC arm. The sample size for subjects with TPS≥50% is targeted at approximately 530, and the overall sample size for this study is projected to be approximately 1240. The number of randomized subjects with TPS≥50% drives the end of enrollment.

[redacted]

8.1.5 Interim Analysis

Two interim analyses are currently planned in this trial. Table 8 provides the summary of the strategy and timing of the interim and final analyses. Details of interim analyses are provided in the DMC Charter.

Table 8 Summary of Interim and Final Analysis Strategy

Analysis	Targeted Number of Events/Targeted Study Time	Expected Approximate Timing of Analysis (from study start)	Primary Purpose
IA1	• At least 250 deaths observed in two arms in the subjects with TPS≥50% AND at least 6 month after last subject is enrolled	• [redacted]	• Demonstrate superiority of pembrolizumab in OS
IA2	• About 38 months after study start (ie, first subject randomized)	• About 38 months	• Demonstrate superiority of pembrolizumab in OS
FA	• [redacted]	• [redacted]	• Demonstrate superiority of pembrolizumab in OS

8.2 Statistical Analysis Plan

8.2.1 Responsibility for Analyses/In-House Blinding

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

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

Although the trial is open-label, analyses or summaries generated by randomized treatment assignment, actual treatment received, and/or PD-L1 biomarker status will be limited and documented. In addition, the independent radiologist(s) will perform the central imaging review without knowledge of treatment group assignment.

The study team at the Sponsor consisting of clinical, statistical, statistical programming and data management personnel, will be blinded to subject-level PD-L1 biomarker results. An unblinded Sponsor clinical scientist, unblinded data management analyst, unblinded Sponsor statistician and unblinded Sponsor statistical programmer will have access to the subject-level PD-L1 results for the purpose of data review and will have no other responsibilities associated with the study. A summary of PD-L1 biomarker prevalence may be provided to the study team at the Sponsor by the IVRS vendor, the unblinded Sponsor clinical scientist or the unblinded Sponsor statistician.

Access to the allocation schedule and the subject-level PD-L1 results for summaries or analyses for presentation to the eDMC will be restricted to an unblinded external statistician, and, as needed, an external scientific programmer performing the analysis, who will have no other responsibilities associated with the study.

Planned interim analyses are described in Section 8.2.9. The eDMC will serve as the primary reviewer of the unblinded results of the interim analyses and will make recommendations for discontinuation of the study or modification to an Executive Oversight Committee of the Sponsor. Depending on the recommendation of the eDMC, the Sponsor may prepare a regulatory submission. If the eDMC recommends modifications to the design of the protocol or discontinuation of the study, this executive oversight committee may be unblinded to results at the treatment level in order to act on these recommendations. Additional logistical details and data monitoring guidance will be provided in the eDMC Charter. Key aspects of the interim analyses are described in Section 8.2.9.

8.2.2 Hypotheses/Estimation

Objectives and hypotheses of the study are stated in Section 3.0. Due to the gate-keeping procedure where the OS hypothesis in the subjects with TPS≥50% will be tested first, the study is considered to have met its primary objective in the primary population of the subjects with TPS≥50% if the pembrolizumab arm is superior to the SOC arm in OS at an interim analysis or the final analysis.

8.2.3 Analysis Endpoints

8.2.3.1 Efficacy Endpoints

Primary

Overall Survival

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

Secondary

Progression-Free Survival – RECIST 1.1

Progression-free survival (PFS) is defined as the time from randomization to the first documented disease progression per RECIST 1.1 based on blinded independent radiologists' assessment or death due to any cause, whichever occurs first. See Section 8.2.5.1.1 for definition of censoring.

Objective Response Rate – RECIST 1.1

Objective response rate (ORR) is defined as the proportion of the subjects in the analysis population who have a confirmed complete response (CR) or partial response (PR) per RECIST 1.1 based on blinded independent radiologists' assessment.

Exploratory

For subjects who demonstrated confirmed CR or PR, response duration is defined as the time from the first documented evidence of CR or PR until disease progression. Response duration for subjects who have not progressed or died at the time of analysis will be censored at the date of their last tumor assessment. ORR based on investigator's assessed RECIST 1.1 will be examined.

PFS by investigator's assessed RECIST 1.1 will also be one of the exploratory endpoints.

PFS2, defined as the time from randomization to subsequent disease progression after initiation of new anti-cancer therapy, or death from any cause, whichever first, will be carried out. If progression after next-line therapy cannot be measured, a PFS event is defined as end or discontinuation of next-line treatment or death from any cause, whichever occurs first. Subjects alive and for whom a PFS event has not been observed will be censored at the last time known to be alive and without second disease progression.

8.2.3.2 Safety Endpoints

Safety measurements are described in Section 7.0 – Trial Procedures.

8.2.4 Analysis Population

8.2.4.1 Efficacy Analysis Population

The primary efficacy analysis will be carried out in the intention-to-treat (ITT) population, i.e., subjects alive at the time of randomization will be included in the treatment group to which they are randomized with TPS≥50%, TPS≥20% and TPS≥1%. Details on the approach to handling missing data are provided in Section 8.2.5 Statistical Methods.

8.2.4.2 Safety Analysis Populations

The primary safety analysis will be based on the All Subjects as Treated (ASaT) population with TPS≥1%.

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 trial treatment they actually received for the analysis of safety data. Subjects who take incorrect trial treatment for the entire treatment period will be included in the treatment group corresponding to the trial treatment actually received. At least one laboratory or vital sign measurement obtained subsequent to at least one dose of trial treatment is required for inclusion in the analysis of each specific parameter. To assess change from baseline, a baseline measurement is also required.

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

8.2.5 Statistical Methods

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

8.2.5.1 Statistical Methods for Efficacy Analyses

The strategy to address multiplicity issues with regard to multiple efficacy endpoints and interim analyses is described in Section 8.2.6 and Section 8.2.9.

8.2.5.1.1 Overall Survival (OS)

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

As an exploratory analysis, recognized methods, e.g., the Rank Preserving Structural Failure Time (RPSFT) model [72], two-stage method, etc., will be used to adjust for the effect of crossover on OS based upon the appropriateness of the data to the assumption required by the methods. The RPSFT model provides a randomization-based estimate of treatment effect (RBEE) corrected for the bias induced by crossover. The 95% confidence intervals of the hazard ratio for OS after adjustment of the effect of crossover will be provided. The Kaplan-Meier estimates of the OS rate at 6 months, 1 year, and other time points of interest will also be compared between the two treatment groups to explore the confounding effect of subsequent treatments. To further account for the possible confounding effect, a sensitivity analysis of OS that censors subjects at the time of initiation of new therapy will be performed and an OS analysis that treats initiation of new therapy as a time-dependent binary covariate will also be conducted. In case the proportional hazards assumption does not hold, Fleming and Harrington's weighted log-rank test, Restricted Mean Survival Time (RMST) method or other methods, as appropriate, will be conducted, possibly after proper adjustment of the crossover effect over time.

8.2.5.1.2 Progression-Free Survival (PFS)

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

Since disease progression is assessed periodically, progressive disease (PD) can occur any time in the time interval between the last assessment where PD was not documented and the assessment when PD is documented. In 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 documented based on blinded central independent radiologists' assessment per RECIST 1.1, regardless of discontinuation of study drug. Death is always considered as a confirmed PD event.

In order to evaluate the robustness of the PFS endpoint, we will perform two sensitivity analyses with a different set of censoring rules. The first sensitivity analysis is the same as the primary analysis except that it censors at the last disease assessment without PD when PD or death is documented after more than one missed disease assessment. The second sensitivity analysis is the same as the primary analysis except that it considers discontinuation of treatment or initiation of new anticancer treatment, whichever occurs later, to be a PD event for subjects without documented PD or death. The censoring rules for primary and sensitivity analyses are summarized in Table 9. In case there is an imbalance between the treatment groups on disease assessment schedules or censoring patterns, we will also perform the following two additional PFS sensitivity analyses: 1) a PFS analysis using time to scheduled tumor assessment visit from randomization as opposed to actual tumor

assessment time; 2) Finkelstein's likelihood-based score test for interval-censored data [73] which modifies the Cox proportional hazard model for interval censored data, will be used as a supportive analysis for the PFS endpoint. The interval will be constructed so that the left endpoint is the date of the last disease assessment without documented PD and the right endpoint is the date of documented PD or death, whichever occurs earlier. In case the proportional hazards assumption does not hold, Fleming and Harrington's weighted log-rank test, Restricted Mean Survival Time (RMST) method or other methods, as appropriate, may be conducted.

Table 9 Censoring Rules for Primary and Sensitivity Analyses of PFS

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

As a supportive analysis, PFS by investigator's assessed RECIST 1.1 will be also carried out.

8.2.5.1.3 Objective Response Rate (ORR)

Stratified Miettinen and Nurminen's method [74] with weights proportional to the stratum size will be used for comparison of the ORR between the treatment arms. A 95% CI for the difference in response rates between the pembrolizumab arm and the control arm will be provided. The stratification factors used for randomization will be applied to the analysis.

8.2.5.1.4 Exploratory Analyses

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

An exploratory analysis of PFS2, defined in Section 8.2.5.1.2, will be carried out using the Kaplan-Meier method, stratified log-rank test and stratified Cox model with Efron's tie handling method for estimation.

8.2.5.2 Statistical Methods for Safety Analyses

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

The analysis of safety results will follow a tiered approach (Table 10). The tiers differ with respect to the analyses that will be performed. Safety parameters or adverse experiences of special interest that are identified *a priori* constitute "Tier 1" safety endpoints that will be subject to inferential testing for statistical significance with p-values and 95% confidence intervals provided for between-group comparisons. For this protocol, there are no Tier 1 AEs. Other safety parameters will be considered Tier 2 or Tier 3. Tier 2 parameters will be assessed via point estimates with 95% confidence intervals provided for between-group comparisons; only point estimates by treatment group are provided for Tier 3 safety parameters.

Adverse experiences (specific terms as well as system organ class terms) and predefined limits of change in laboratory, vital signs, and ECG parameters that are not pre-specified as Tier 1 endpoints will be classified as belonging to "Tier 2" or "Tier 3", based on the number of events observed. Membership in Tier 2 requires that at least 4 subjects in any treatment group exhibit the event; all other adverse experiences and predefined limits of change will belong to Tier 3.

The threshold of at least 4 events was chosen because the 95% confidence interval for the between-group difference in percent incidence will always include zero when treatment groups of equal size each have less than 4 events and thus would add little to the interpretation of potentially meaningful differences. Because many 95% confidence intervals may be provided without adjustment for multiplicity, the confidence intervals should be regarded as a helpful descriptive measure to be used in review, not a formal method for assessing the statistical significance of the between-group differences in adverse experiences and predefined limits of change.

Continuous measures such as changes from baseline in laboratory, vital signs, and ECG parameters will be considered Tier 3 safety parameters. Summary statistics for baseline, on-treatment, and change from baseline values will be provided by treatment group in table format.

To properly account for the potential difference in follow-up time between the study arms, which is expected to be longer in the pembrolizumab arm, an analysis of Grade 3-5 AEs will be based on the time to first event using the same time-to-event analysis methods as for OS (i.e., the stratified log-rank test will be used for testing the time to AEs, and the Cox model with Efron's tie handling method will be used for estimating the hazard ratio and its 95%

confidence interval). For other AEs with potentially differential follow-up time, such analysis may also be explored.

In addition, the broad clinical and laboratory AE categories consisting of the percentage of subjects with any AE, any drug-related AE, any Grade 3-5 AE, any serious AE, any AE which is both drug related and Grade 3-5, any AE which is both serious and drug-related, dose modification due to AE, and who discontinued due to an AE, and death will be considered Tier 2 endpoints. 95% confidence intervals (Tier 2) will be provided for between-treatment differences in the percentage of subjects with events; these analyses will be performed using the Miettinen and Nurminen method. Detailed kinetics and characteristics of immune-mediated AEs will be summarized separately in the study.

Based on emerging external data, the analysis strategy for safety parameters may be modified to improve the integrity and efficiency of the design. Should this happen, the change will be documented elsewhere, if not in a protocol amendment, at the earliest time before any unblinding of the data.

Table 10 Analysis Strategy for Safety Parameters

Safety Tier	Safety Endpoint	p-Value	95% CI for Treatment Comparison	Descriptive Statistics
Tier 2	Any AE		X	X
	Any Grade 3-5 AE		X	X
	Any Serious AE		X	X
	Onset and Duration of First Grade 3-5 AE		X	X
	Any Drug-Related AE		X	X
	Any Serious and Drug-Related AE		X	X
	Any Grade3-5 and Drug-Related AE		X	X
	Dose Modification Due to AE		X	X
	Discontinuation Due to AE		X	X
	Death		X	X
	Specific AEs, SOCs (including ≥4 of subjects in one of the treatment groups)		X	X
Tier 3	Specific AEs, SOCs (incidence <4 of subjects in all of the treatment groups)			X
	Change from Baseline Results (Labs, ECGs, Vital Signs)			X
There are no Tier 1 AEs pre-specified in this protocol.				

8.2.5.3 Summaries of Baseline Characteristics, Demographics, and Other Analyses

The comparability of the treatment groups for each relevant baseline characteristic will be assessed by the use of tables and/or graphs. No statistical hypothesis tests will be performed on these characteristics. The number and percentage of subjects randomized and the primary reason for discontinuation will be displayed. Demographic variables (such as age) and

baseline characteristics will be summarized by treatment either by descriptive statistics or categorical tables in subjects with TPS≥50%, TPS≥20%, and TPS≥1%. The reasons for exclusion from the ITT population (if any) will be summarized.

8.2.6 Multiplicity

The multiplicity strategy specified in this section will be applied to the subjects with TPS≥50%, TPS≥20%, and TPS≥1% for the testing of the OS, PFS, and ORR hypotheses. The overall type I error is strongly controlled at 2.5% (one-sided). The hypotheses will be tested sequentially at the type I error rate of 2.5% (one-sided) in the following order: superiority of pembrolizumab in OS in the subjects with TPS≥50%, superiority of pembrolizumab in OS in the subjects with TPS≥20%, superiority of pembrolizumab in OS in the subjects with TPS≥1%, superiority of pembrolizumab in PFS in the subjects with TPS≥50%, superiority of pembrolizumab in PFS in the subjects with TPS≥20%, superiority of pembrolizumab in PFS in the subjects with TPS≥1%, superiority of pembrolizumab in ORR in the subjects with TPS≥50%, superiority of pembrolizumab in ORR in the subjects with TPS≥20%, and superiority of pembrolizumab in ORR in the subjects with TPS≥1%. Under this sequential testing strategy, a hypothesis will be tested only if superiority is established for all the preceding ones.

The initial alpha allocation is revised to reflect the change of the criteria for the conduct of the FA and the addition of IA2. The reallocation of alpha occurs after the conduct of IA1, and proper adjustment is made to maintain the control of family-wise type I error rate with the implementation of this change. The type I error actually spent at IA1 will be kept intact and the re-allocation will only be applied to the remaining unspent alpha. No futility boundary will be set as before.

[redacted]

If the pembrolizumab arm demonstrates superior OS in the subjects with TPS≥50% at an interim or final analysis, the OS hypothesis in the subjects with TPS≥20% will be tested based on a group sequential approach with the cumulative alpha spent up to each interim analysis at the same level as the alpha spent for testing the OS hypothesis in the subjects with TPS≥50% up to that analysis [71]. Note that, based on the above sequential testing strategy, if the OS superiority is demonstrated at an interim analysis in the subjects with TPS≥50%,

the OS superiority in the subjects with TPS≥20% may be demonstrated at a later analysis. If the pembrolizumab arm demonstrates superior OS in the subjects with both TPS≥50% and TPS≥20%, the OS hypothesis in the subjects with TPS≥1% will be tested using the same approach.

Testing of the PFS hypotheses will be performed at the same interim analyses and FA. The cumulative alpha spending is determined by the same alpha spending function (on the scale of calendar time) defined above for the OS hypotheses. The corresponding stopping bounds for PFS at IA2 and FA will then be calculated based on the actual number of deaths observed at each analysis. Statistical significance under multiplicity control can only be established once the OS hypotheses have been established at an interim or final analysis. Otherwise, nominal p-values will be reported as a measure of strength of association for the PFS hypotheses.

Testing of the ORR hypotheses will be based on the IA1 data. Statistical significance under multiplicity control can only be established once the OS and PFS hypotheses have both been established. Otherwise, nominal p-values will be reported as a measure of strength of association for the ORR hypotheses. If OS and PFS are not statistically significant at IA1, then the ORR at IA1 will be considered without any data update if the step-down criteria allow formal testing based on a later analysis of OS and PFS.

8.2.7 Sample Size and Power Calculation

The study will randomize subjects in a 1:1 ratio into the pembrolizumab arm and the SOC arm. The sample size for the subjects with TPS≥50% is targeted at approximately 530, and the overall sample size for this study is projected to be approximately 1240. The number of randomized subjects with TPS≥50% drives the end of enrollment.

cci [redacted] .

cci [redacted]

[redacted]

8.2.8 Subgroup Analyses and Effect of Baseline Factors

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

- Age category (≤65 vs. >65 years)
- Sex (female vs. male)
- Race (white vs. non-white)
- ECOG status (0 vs. 1)
- Geographic region of enrolling site (East Asia vs. non-East Asia and East Asia vs. Europe vs. Latin America vs. Other)
- Histology (squamous vs. non-squamous)
- Smoking status (never vs. former vs. current)
- PD-L1 status (TPS≥50% vs. TPS 1-49%, TPS≥20% vs. TPS 1-19%, and TPS≥50% vs. TPS 20-49% vs. TPS 1-19%)
- Investigators' choice of standard of care chemotherapy prior to randomization (Pemetrexed vs. No Pemetrexed)
- Disease stage (advanced vs. metastatic)
- Brain metastasis status (baseline brain metastasis vs. no baseline brain metastasis)
- Baseline tumor size (at/above median vs. below median)

The consistency of the treatment effect will be assessed descriptively via summary statistics by category for the classification variables listed above. These subgroup analyses will be carried out in the subjects with TPS≥50%, TPS≥20%, and TPS≥1%.

8.2.9 Interim Analyses

There are 2 planned interim analyses. The totality of the data from the interim analyses will be reviewed by a data monitoring committee (DMC). Further details of interim analyses are provided below. Table 11 summarizes the timing, target events, and decision guidance for the interim and final OS analyses based on the projected number of deaths in subjects with

TPS≥50%, TPS≥20% and TPS≥1%. These details will be incorporated into the DMC Charter.

The IA1 will be conducted after at least 250 deaths are observed between the pembrolizumab arm and control arm in the subjects with TPS≥50% and at least 6 months after last subject enrolled. Any change to the timing, along with its rationale, will be documented in a memo to the study file before the database lock for IA1.

The IA2 will be conducted about 38 months after first subject randomized (study start). By then, about 340 deaths are projected to occur in the subjects with TPS≥50%. The boundary nominal alpha can then be calculated based on the actual number of deaths observed at IA1 and IA2 with the cumulative alpha determined by the Hwang-Shih-DeCani alpha spending function with the gamma parameter -0.9023 on the scale of calendar time. If the OS superiority is demonstrated in the subjects with TPS≥50%, the OS hypotheses in the subjects with TPS≥20% and TPS≥1% will be tested based on a group sequential approach with the cumulative alpha spent up to each interim analysis the same as the alpha spent for testing the OS hypothesis in the subjects with TPS≥50% up to that interim analysis. The projected numbers of deaths at IA2 are 474 and 780 in subjects with TPS≥20% and TPS≥1%, respectively.

Table 11 Decision Guidance for the Primary OS Hypotheses at the Interim Analyses and Final Analysis under a Hypothetical Scenario

Analysis	Targeted Number of Events/Targeted Study Time	Cumulative Alpha	Efficacy Bars in Subjects with TPS≥50%[1]	Efficacy Bars in Subjects with TPS≥20% (if OS positive in TPS≥50%)[1]	Efficacy Bars in Subjects with TPS≥1% (if OS positive in both TPS≥50% and TPS≥20%)[1]
IA1	• At least 250 deaths observed in two arms in the subjects with TPS≥50% AND at least 6 month after last subject is enrolled (~32 months after study start) • [redacted]	• 1.576%	• (One-sided) p-value for OS < 1.576%, i.e., observed HR < ~0.78 (~3.7-month improvement)	• (One-sided) p-value for OS < 1.576%, i.e., observed HR < ~0.81 (~3.1-month improvement)	• (One-sided) p-value for OS < 1.576%, i.e., an observed HR < ~0.85 (2.3-month improvement)
IA2	• About 38 months after study start[2]	• 1.94%	• (One-sided) p-value for OS < 1.233%, i.e., observed HR < ~0.78 (3.6-month improvement)	• (One-sided) p-value for OS < 1.197%, i.e., observed HR < ~0.81 (3.0-month improvement)	• (One-sided) p-value for OS < 1.228%, i.e., observed HR < ~0.85 (2.3-month improvement)
FA	• [redacted]	• 2.5%	• (One-sided) p-value for OS < 1.521%, i.e., observed HR < ~0.80 (3.2-month improvement)	• (One-sided) p-value for OS < 1.497%, i.e., observed HR < ~0.83 (2.6-month improvement)	• (One-sided) p-value for OS < 1.556%, i.e., observed HR < ~0.87 (2.0-month improvement)

[1] [redacted]

[2] Study start is defined as the date when the first subject was randomized.

8.2.10 Compliance (Medication Adherence)

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

8.2.11 Extent of Exposure

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

9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.1 Investigational Product

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

All supplies indicated in Table 12 will be provided per the "Source/Additional Information" column depending on local country operational requirements.

Any commercially available product not included in Table 12 will be provided by the trial site, subsidiary or designee.

Table 12 Product Descriptions

Product Name & Potency	Dosage Form	Source/Additional Information
Pembrolizumab 100 mg/4 mL	Injection	Provided centrally by the Sponsor
Carboplatin 10 mg/mL, 60 mL	Injection	Provided centrally by the Sponsor or locally by the trial site, subsidiary, or designee
Paclitaxel 6 mg/mL, 16.7 mL	Injection	Provided centrally by the Sponsor or locally by the trial site, subsidiary, or designee
Pemetrexed 500 mg/vial	Injection	Provided centrally by the Sponsor or locally 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 will be responsible for recording the lot number, manufacturer and expiry date of 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.

Subjects will receive open label vials or kits. All kitted products will contain 1 vial per kit box.

9.3 Clinical Supplies Disclosure

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

9.4 Storage and Handling Requirements

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

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

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

9.5 Returns and Reconciliation

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

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

9.6 Standard Policies

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

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

10.1 Confidentiality

10.1.1 Confidentiality of Data

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

10.1.2 Confidentiality of Subject Records

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

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

10.1.3 Confidentiality of Investigator Information

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

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

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

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

10.1.4 Confidentiality of IRB/IEC Information

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

10.2 Compliance with Financial Disclosure Requirements

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

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

10.3 Compliance with Law, Audit and Debarment

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

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

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

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

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

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

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

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

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

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

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

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

10.4 Compliance with Trial Registration and Results Posting Requirements

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

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

10.5 Quality Management System

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

10.6 Data Management

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

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

10.7 Publications

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

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

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

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

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

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12.0 APPENDICES

12.1 Merck Code of Conduct for Clinical Trials

Merck*
Code of Conduct for Clinical Trials

I. Introduction

A. Purpose

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

B. Scope

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

II. Scientific Issues

A. Trial Conduct

1. Trial Design

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

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

2. Site Selection

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

3. Site Monitoring/Scientific Integrity

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

B. Publication and Authorship

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

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

III. Subject Protection

A. IRB/ERC review

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

B. Safety

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

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

C. Confidentiality

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

D. Genomic Research

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

IV. Financial Considerations

A. Payments to Investigators

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

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

B. Clinical Research Funding

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

C. Funding for Travel and Other Requests

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

V. Investigator Commitment

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

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

12.2 Collection and Management of Specimens for Future Biomedical Research

1. Definitions

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

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

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

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research

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

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

3. Summary of Procedures for Future Biomedical Research

a. Subjects for Enrollment

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

b. Informed Consent

Informed consent for specimens (i.e., DNA, RNA, protein, etc.) will be obtained during screening for protocol enrollment from all subjects or legal guardians, at a trial visit by the investigator or his or her designate. Informed consent for Future Biomedical Research should be presented to the subjects on Visit 1. If delayed, present consent at next possible Subject Visit. Informed consent must be obtained prior to collection of all Future Biomedical Research specimens. Consent forms signed by the subject will be kept at the clinical trial site under secure storage for regulatory reasons. Information contained on the consent form alone cannot be traced

to any specimens, test results, or medical information once the specimens have been rendered de-identified.

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

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

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

c. eCRF Documentation for Future Biomedical Research Specimens

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

d. Future Biomedical Research Specimen Collections

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

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

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

4. Confidential Subject Information for Future Biomedical Research

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

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

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

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

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

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

5. Biorepository Specimen Usage

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

Analyses utilizing the Future Biomedical Research specimens may be performed by Merck, or an additional third party (e.g., a university investigator) designated by Merck. The investigator conducting the analysis will be provided with double coded specimens. Re-association of analysis results with corresponding clinical data will only be conducted

by the Merck Entrusted Keyholder. Any contracted third party analyses will conform to the specific scope of analysis outlined in this sub-trial. Future Biomedical Research specimens remaining with the third party after the specific analysis is performed will be returned to the sponsor or destroyed and documentation of destruction will be reported to Merck.

6. Withdrawal From Future Biomedical Research

Subjects may withdraw their consent for Future Biomedical Research and have their specimens and all derivatives destroyed. Subjects may withdraw consent at any time by contacting the principal investigator for the main trial. If medical records for the main trial are still available, the investigator will contact Merck using the designated mailbox PPD and a form will be provided by Merck to obtain appropriate information to complete specimen withdrawal. Subsequently, the subject's specimens will be removed from the biorepository and be destroyed. A letter will be sent from Merck to the investigator confirming the destruction. It is the responsibility of the investigator to inform the subject of completion of destruction. Any analyses in progress at the time of request for destruction or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research trial data and results. No new analyses would be generated after the request is received.

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

7. Retention of Specimens

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

Specimens from the trial site will be shipped to a central laboratory and then shipped to the Merck designated biorepository. The specimens will be stored under strict supervision in a limited access facility which operates to assure the integrity of the specimens. Specimens will be destroyed according to Merck policies and procedures and this destruction will be documented in the biorepository database.

8. Data Security

Separate databases for specimen information and for results from the Future Biomedical Research sub-trial will be maintained by Merck. This is done to separate the future exploratory test results (which include genetic data) from the clinical trial database thereby maintaining a separation of subject number and these results. The separate databases are accessible only to the authorized Sponsor and the designated trial administrator research personnel and/or collaborators. Database user authentication is

highly secure, and is accomplished using network security policies and practices based in international standards (e.g., ISO17799) to protect against unauthorized access. The Merck Entrusted Keyholder maintains control over access to all specimen data. These data are collected for future biomedical research purposes only as specified in this sub-trial will not be used for any other purpose.

9. Reporting of Future Biomedical Research Data to Subjects

There is no definitive requirement in either authoritative ethical guidelines or in relevant laws/regulations globally that research results have to be, in all circumstances, returned to the trial participant. Some guidelines advocate a proactive return of data in certain instances. No information obtained from exploratory laboratory studies will be reported to the subject or family, and this information will not be entered into the clinical database maintained by Merck on subjects. Principle reasons not to inform or return results to the subject include: lack of relevance to subject health, limitations of predictive capability, concerns of misinterpretation and absence of good clinical practice standards in exploratory research typically used for diagnostic testing.

If any exploratory results are definitively associated with clinical significance for subjects while the clinical trial is still ongoing, investigators will be contacted with information as to how to offer clinical diagnostic testing (paid for by Merck) to subjects enrolled and will be advised that counseling should be made available for all who choose to participate in this diagnostic testing.

If any exploratory results are definitively associated with clinical significance after completion of a clinical trial, Merck will publish the results without revealing specific subject information, inform all trial sites who participated in the Merck clinical trial and post anonymized results on our website or other accredited website(s) that allow for public access (e.g., disease societies who have primary interest in the results) in order that physicians and patients may pursue clinical diagnostic testing if they wish to do so.

10. Gender, Ethnicity and Minorities

Although many diagnoses differ in terms of frequency by ethnic population and gender, every effort will be made to recruit all subjects diagnosed and treated on Merck clinical trials for future biomedical research. When trials with specimens are conducted and subjects identified to serve as controls, every effort will be made to group specimens from subjects and controls to represent the ethnic and gender population representative of the disease under current investigation.

11. Risks Versus Benefits of Future Biomedical Research

For future biomedical research, risks to the subject have been minimized. Risks include those associated with venipuncture to obtain the whole blood specimen. This specimen will be obtained at the time of routine blood specimens drawn in the main trial.

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

It is necessary for subject-related data (i.e., ethnicity, diagnosis, drug therapy and dosage, age, toxicities, etc.) to be re-associated to double coded specimens at the time of data analysis. These subject data will be kept in a separate, secure Merck database, and all specimens will be stripped of subject identifiers. No information concerning results obtained from future biomedical research will be entered into clinical records, nor will it be released to outside persons or agencies, in any way that could be tied to an individual subject.

12. Self-Reported Ethnicity

Subjects who participate in future biomedical research will be asked to provide self-reported ethnicity. Subjects who do not wish to provide this data may still participate in future biomedical research.

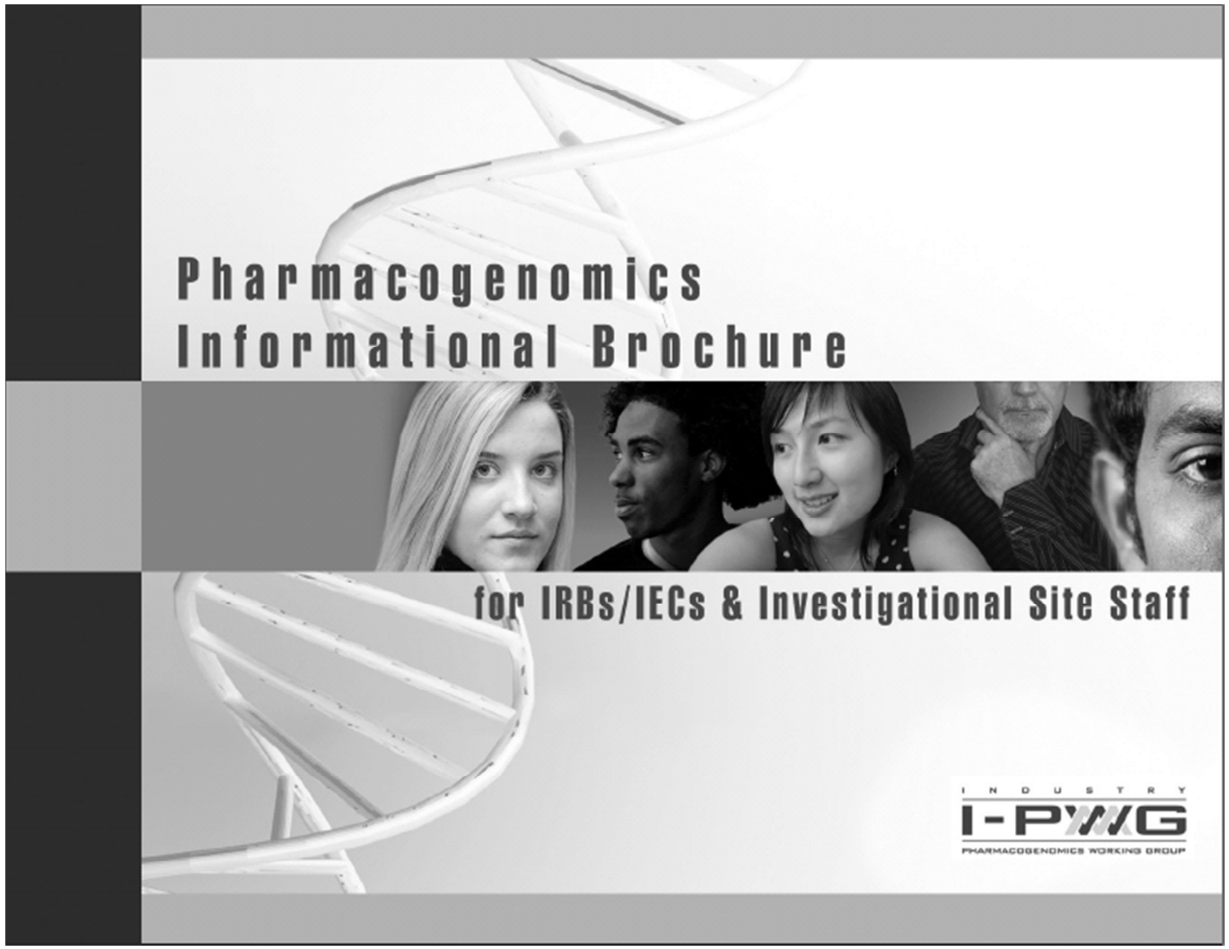
13. Questions

Any questions related to the future biomedical research should be e-mailed directly to PPD .

14. References

1. National Cancer Institute: http://www.cancer.gov/dictionary/?searchTxt=biomarker
2. International Conference on Harmonization: DEFINITIONS FOR GENOMIC BIOMARKERS, PHARMACOGENOMICS, PHARMACOGENETICS, GENOMIC DATA AND SAMPLE CODING CATEGORIES - E15; http://www.ich.org/LOB/media/MEDIA3383.pdf

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



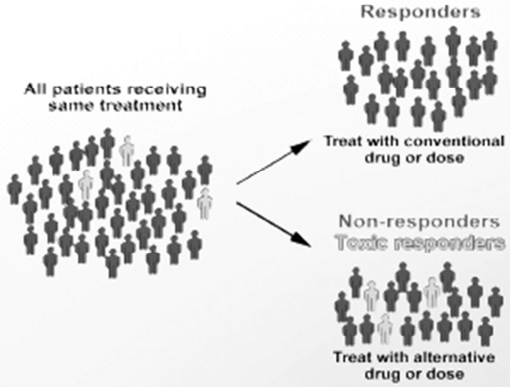
This Informational Brochure is intended for IRBs/IECs & Investigational Site Staff. The brochure was developed to address issues relevant to DNA collection and research in the context of pharmaceutical drug development.

Developed by
The Industry Pharmacogenomics Working Group (I-PWG)
www.i-pwg.org

What is DNA and What is Pharmacogenomics?

The cells of the body contain **deoxyribonucleic acid (DNA)**. DNA is inherited, and carries a code (in the form of **genes**), which determines physical appearance and other personal features. In a process called gene transcription, DNA is copied into a related molecule, ribonucleic acid (RNA), before ultimately being translated into proteins, which determine cellular function. Naturally-occurring variation in DNA is a major determinant of differences among people. This variation, referred to as **genetic polymorphism**, occurs both within genes and outside of genes throughout the entire **human genome**. This variation partly explains why some people develop certain diseases and others do not, why some people respond better than others to certain drugs, and why some people develop side effects while others do not.

Pharmacogenomics (PGx) is a branch of science that uses genetic/genomic information to better understand why people respond differently to drugs. The terms **pharmacogenomics** and **pharmacogenetics** are often used interchangeably, although pharmacogenetics generally refers to the study of DNA, while pharmacogenomics is a broader term encompassing the study of both DNA and RNA[1], and generally on a larger scale. Pharmacogenomic research is different from **genetic testing** done for the purpose of diagnosing a person with a certain disease or for risk for developing a certain disease (e.g., genetic testing for Huntington's Disease). PGx focuses on genetic variability that affects response to drugs. This primarily occurs through pathways related to drug metabolism, drug mechanism of action, disease etiology or subtype, and adverse events. PGx overlaps with **disease genetics** research since different disease subtypes can respond differently to drugs.



Why is Pharmacogenomics Important?

PGx is one approach to explore whether a drug will be useful or harmful in certain people. By identifying genetic polymorphisms that are associated with drug efficacy and safety, PGx is allowing for more individualized drug therapies based on the genetic makeup of patients. This is sometimes referred to as **personalized medicine**. By better understanding diseases at the molecular level, PGx is opening opportunities for the discovery of novel drugs.

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PGx has the overarching goal of developing safer, more effective drugs, and ensuring that patients receive the correct dose of the correct drug at the correct time.

How is Pharmacogenomics Being Used in Drug Development?

PGx is increasingly becoming a core component of drug development programs. By using PGx to determine how drugs work differently in subgroups of patients, drug developers are making better decisions about which drugs to develop and how best to develop them. Technologies are now available to simultaneously analyze over 1 million genetic polymorphisms in the human genome. This is allowing for the identification of novel genetic markers of drug response and of disease in absence of pre-existing knowledge of the involvement of specific pathways.

PGx research is currently being used in drug development to:

- Explain variability in response among subjects in clinical trials
- Address emerging clinical issues, such as unexpected adverse events
- Determine eligibility for clinical trials (pre-screening) to optimize trial design
- Develop drug-linked diagnostic tests to identify patients who are more likely or less likely to benefit from treatment or who may be at risk of adverse events
- Better understand the mechanism of action or metabolism of new and existing drugs
- Provide better understanding of disease mechanisms
- Allow physicians to prescribe the right drugs at the optimal dose for individual patients

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Pharmacogenomics Already a Reality in Drug Labels

A number of drugs now have instructions on their labels either recommending or requiring a PGx test when prescribing a drug or when making dosing decisions. A well-known example is the anti-coagulant drug *warfarin*. The drug label for warfarin now includes a recommended PGx test to minimize the risk of excessive bleeding (US label). There are currently three categories of PGx information in drug labels according to the FDA:

i) tests **required** for prescribing

ii) tests **recommended** when prescribing

iii) PGx information **for information only**.

For a current list of examples of how PGx is impacting drug labeling see:
www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm

DNA Samples from Clinical Trials An Invaluable Resource

Adequate sample sizes and high-quality clinical data are key to advancements in the field of PGx. Drug development programs are therefore an invaluable resource and a unique opportunity for highly productive research in PGx. Although PGx is a rapidly evolving branch of science, the complexities of the genetic code are only beginning to be understood. As scientific discoveries continue to be made, samples collected today will become a valuable resource

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for future research. This may lead to the future development of new drugs that are better targeted to certain individuals and to disease subtypes.

For these reasons, it is vital to systematically collect DNA samples across all centers recruiting subjects into clinical trials that include a PGx component (where local regulations permit). Consent for storage of samples for future research should also be obtained if maximum benefit is to be derived from DNA samples donated by subjects. The scope of the research that may be performed both during the trial and in the future should be clearly defined in the informed consent form.

Informed Consent

Policies and regulations for legally effective informed consent vary on national, state, and local levels. There currently are no internationally recognized regulations that dictate the basic elements of informed consent for PGx research. The I-PWG has published an article on the elements of informed consent to be considered in PGx research studies[2]. These elements build upon existing basic elements of informed consent for clinical research on human subjects[3].

Return of Genomic Research Results to Study Subjects

Policies for the return of genomic results to study subjects vary among pharmaceutical companies. There are many considerations that pharmaceutical companies weigh when determining their policy regarding the return of PGx research results to study subjects. These include i) the conditions under which genomic results were generated (i.e., research laboratory environment versus accredited diagnostic laboratory), ii) whether the results will have an impact on patient medical care, iii) whether genetic counseling is necessary, and iv) international, national, and local guidelines, policies, legislation, and regulations regarding subjects' rights to access data generated on them. These considerations are addressed in detail in Renegar et al. 2006[4].

Privacy, Confidentiality, and Patient Rights

An issue that is generally perceived to be of relevance to clinical genetic research is the risk associated with inadvertent or intentional disclosure and misuse of genetic data. Although coded specimens generally have been considered adequate to protect patient privacy in most clinical development, companies and other institutions involved in PGx research have historically applied a variety of additional safeguards that can be used alone, or in combination, to further minimize the potential risk of disclosure and misuse of genetic data. These include:

i) Sample Labeling

DNA samples and corresponding clinical data can be labeled in several ways to achieve different levels of patient privacy and confidentiality. Definitions of labeling methods are provided in the glossary and are described in greater detail in the ICH Guidance E15[1]. It is important to recognize that there is a trade-off between the level of patient privacy protection and the ability to perform actions related to withdrawal of consent, data return, clinical monitoring, subject follow-up, and addition of new data (see Table 1)[1]. The *Identified* and *Anonymous* labeling categories described in the table are generally not applicable to pharmaceutical clinical trials.

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Table adapted from ICH Guidance E15

Sample Coding Category		Link Between Subject's Personal Identifiers and Genomic Biomarker Data	Traceability back to the Subject (Actions Possible, Including e.g., Sample Withdrawal or Return of Individual Genomic Results at Subject's Request	Ability to Perform Clinical Monitoring, Subject Follow-up, or Addition of New Data	Extent of Subject's Confidentiality and Privacy Protection
Identified		Yes (Direct) Allows for Subjects to be Identified	Yes	Yes	Similar to General Healthcare Confidentiality and Privacy
Coded	Single	Yes (Indirectly) Allows for Subjects to be Identified (via Single, Specific Coding Key)	Yes	Yes	Standard for Clinical Research
	Double	Yes (Very Indirectly) Allows for Subjects to be Identified (via the Two Specific Coding Keys)	Yes	Yes	Added Privacy and Confidentiality Protection over Single Code
Anonymized		No Does not Allow Subject to be Re-Identified as the Coding-Key(s) Have Been Deleted	No	No	Genomic Data and Samples no Longer Linked to Subject as Coding Key(s) have been Deleted
Anonymous		No – Identifiers Never Collected and Coding Keys Never Applied. Does not Allow for Subjects to be Identified	No	No	Genomic Data and Samples Never Linked to Subject

ii) Separation of Data and Restricted Access

- Maintaining PGx-related documentation separate from other medical records.
- Restricting access to data and samples by means of password-protected databases and locked sample storage facilities.

PGx studies in pharmaceutical development are generally conducted in research laboratories that are not accredited diagnostic laboratories. Therefore, PGx research data usually cannot be used to make clinically meaningful or reliable decisions about a subject's health or health risks. Furthermore, confidentiality protections described above serve to guard against inappropriate disclosure of these data. For these reasons, the potential risk to a subject's employment or health/life insurance is considered to be minimal. The measures taken to protect subjects against reasonably foreseeable risks should be addressed in the informed consent form[2].

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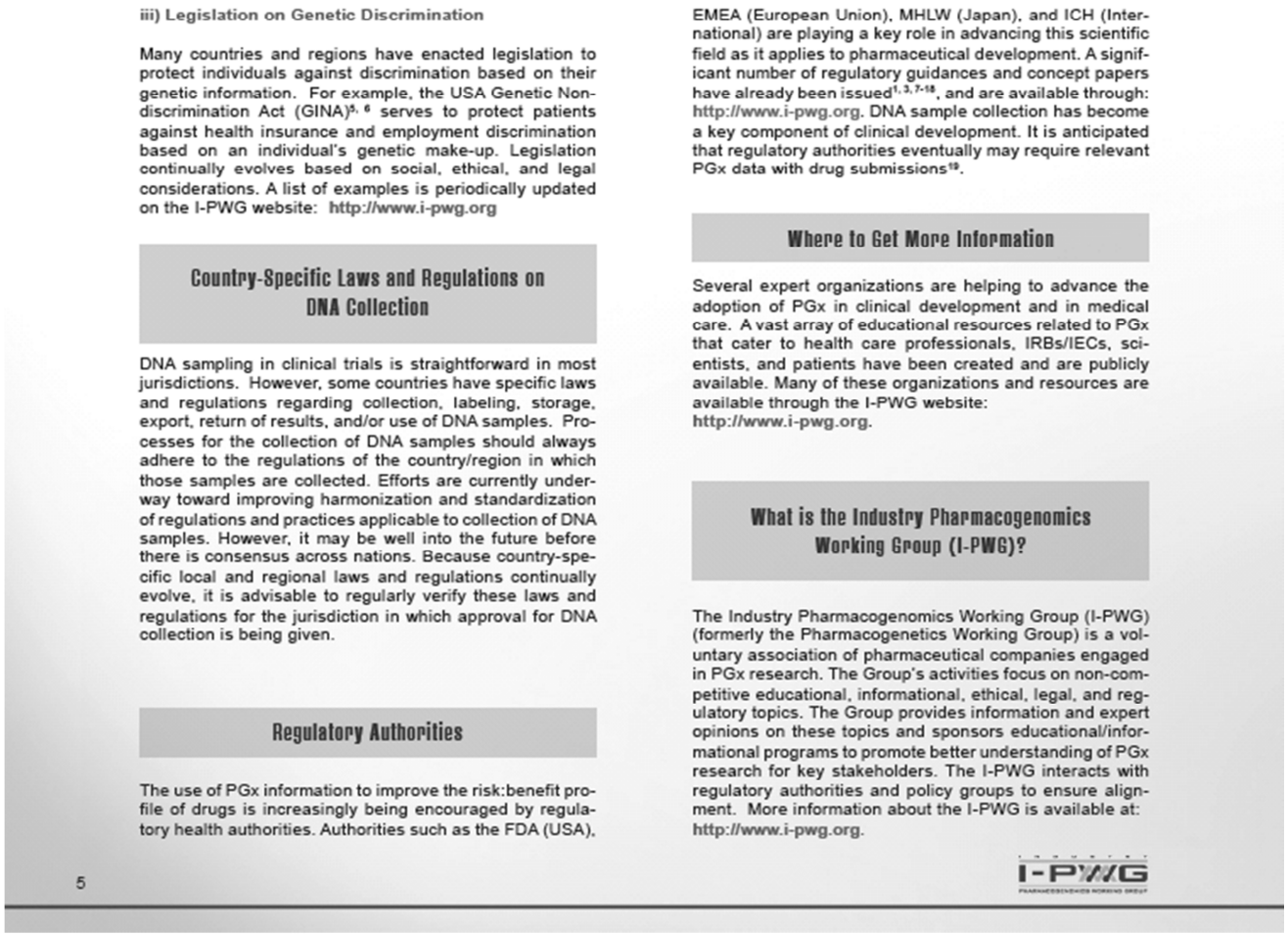

iii) Legislation on Genetic Discrimination

Many countries and regions have enacted legislation to protect individuals against discrimination based on their genetic information. For example, the USA Genetic Non-discrimination Act (GINA)[5, 6] serves to protect patients against health insurance and employment discrimination based on an individual's genetic make-up. Legislation continually evolves based on social, ethical, and legal considerations. A list of examples is periodically updated on the I-PWG website: http://www.i-pwg.org

Country-Specific Laws and Regulations on DNA Collection

DNA sampling in clinical trials is straightforward in most jurisdictions. However, some countries have specific laws and regulations regarding collection, labeling, storage, export, return of results, and/or use of DNA samples. Processes for the collection of DNA samples should always adhere to the regulations of the country/region in which those samples are collected. Efforts are currently underway toward improving harmonization and standardization of regulations and practices applicable to collection of DNA samples. However, it may be well into the future before there is consensus across nations. Because country-specific local and regional laws and regulations continually evolve, it is advisable to regularly verify these laws and regulations for the jurisdiction in which approval for DNA collection is being given.

Regulatory Authorities

The use of PGx information to improve the risk:benefit profile of drugs is increasingly being encouraged by regulatory health authorities. Authorities such as the FDA (USA), EMEA (European Union), MHLW (Japan), and ICH (International) are playing a key role in advancing this scientific field as it applies to pharmaceutical development. A significant number of regulatory guidances and concept papers have already been issued[1, 3, 7-18], and are available through: http://www.i-pwg.org. DNA sample collection has become a key component of clinical development. It is anticipated that regulatory authorities eventually may require relevant PGx data with drug submissions[19].

Where to Get More Information

Several expert organizations are helping to advance the adoption of PGx in clinical development and in medical care. A vast array of educational resources related to PGx that cater to health care professionals, IRBs/IECs, scientists, and patients have been created and are publicly available. Many of these organizations and resources are available through the I-PWG website: http://www.i-pwg.org.

What is the Industry Pharmacogenomics Working Group (I-PWG)?

The Industry Pharmacogenomics Working Group (I-PWG) (formerly the Pharmacogenetics Working Group) is a voluntary association of pharmaceutical companies engaged in PGx research. The Group's activities focus on non-competitive educational, informational, ethical, legal, and regulatory topics. The Group provides information and expert opinions on these topics and sponsors educational/informational programs to promote better understanding of PGx research for key stakeholders. The I-PWG interacts with regulatory authorities and policy groups to ensure alignment. More information about the I-PWG is available at: http://www.i-pwg.org.

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Glossary

Identified Data and Samples: Identified data and samples are labeled with personal identifiers such as name or identification numbers (e.g., social security or national insurance number). The use of identified data and samples allows for clinical monitoring and subject follow-up and are generally not considered appropriate for purposes of clinical trials in drug development. (Not generally applicable to PGx in pharmaceutical clinical trials).

Coded Data and Samples: Coded data and samples are labeled with at least one specific code, and do not carry any personal identifiers.

Single-Coded Data and Samples: are usually labeled with a single specific code. It is possible to trace the data or samples back to a given individual with the use of a single coding key.

Double-Coded (De-identified) Data and Samples: are initially labeled with a single specific code and do not carry any personal identifiers. The data and samples are then relabeled with a second code, which is linked to the first code via a second coding key. It is possible to trace the data or samples back to the individual by the use of both coding keys. The use of the second code provides additional confidentiality and privacy protection for subjects over the use of a single code.

Anonymized Data and Samples: Anonymized data and samples are initially single or double coded but the link between the subjects' identifiers and the unique code(s) is subsequently deleted. Once the link has been deleted, it is no longer possible to trace the data and samples back to individual subjects through the coding key(s). Anonymization is intended to prevent subject re-identification.

Anonymous Data and Samples: Anonymous data and samples are never labeled with personal identifiers when originally collected, nor is a coding key generated. Therefore, there is no potential to trace back genomic data and samples to individual subjects. Due to restrictions on the ability to correlate clinical data with such samples, they are generally of little use to PGx research. (Not generally applicable to PGx in pharmaceutical clinical trials).

6

References

1. ICH E15 - Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories. April 2008. (Accessed at: http://www.fda.gov/OHRMS/DOCKETS/98fr/FDA-2008-D-0199-gdl.pdf and at: http://www.ich.org/LOB/media/MEDIA3383.pdf)

2. Anderson DC, Gomez-Mancilla B, Spear BB, et al. Elements of informed consent for pharmacogenetic research; perspective of the pharmacogenetics working group. Pharmacogenomics Journal 2002;2(5):284-92.

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5. Genetic Information Nondiscrimination Act (GINA): 2007-2008. (Accessed at: http://www.genome.gov/24519851)

6. Hudson KL, Holohan MK, Collins FS. Keeping pace with the times--the Genetic Information Nondiscrimination Act of 2008. New England Journal of Medicine 2008;358(25):2661-3.

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

8. EMEA CHMP Position Paper on Terminology in Pharmacogenetics. June 2003. (Accessed at: http://www.tga.health.gov.au/docs/pdf/euguide/emea/307001en.pdf)

9. EMEA CHMP Reflection Paper on the Use of Pharmacogenetics in the Pharmacokinetic Evaluation of Medicinal Products. May 2007. (Accessed at: http://www.emea.europa.eu/pdfs/human/pharmacogenetics/12851706enfin.pdf)

10. EMEA CHMP Guideline on Pharmacogenetic Briefing Meetings. November 2005. (Accessed at: http://www.emea.europa.eu/pdfs/human/pharmacogenetics/2022704en.pdf)

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11. EMEA CHMP Reflection Paper on Pharmacogenomic Samples, Testing, and Data Handling. November 2007. (Accessed at: http://www.emea.europa.eu/pdfs/human/pharmacogenetics/20191406en.pdf)

12. EMEA CHMP Reflection Paper on the Use of Genomics in Cardiovascular Clinical Intervention Trials. November 2007. (Accessed at: http://www.emea.europa.eu/pdfs/human/pharmacogenetics/27878906enfin.pdf)

13. EMEA CHMP Biomarkers Qualification: Guidance to Applicants. 2008. (Accessed at: http://www.emea.europa.eu/pdfs/human/biomarkers/7289408en.pdf)

14. EMEA CHMP Understanding Terminology Used in Pharmacogenetics July 2004. (Accessed at: http://www.emea.europa.eu/pdfs/human/pharmacogenetics/384204en.pdf)

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

16. FDA. FDA Guidance - Pharmacogenetic Tests and Genetic Tests for Heritable Markers. June 2007. (Accessed at: www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm077862.htm)

17. FDA Guidance - Pharmacogenomic Data Submissions. March 2005. (Accessed at: http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126957.pdf)

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19. Rittenhouse P. Framing DNA collection in the clinic. Biocentury, The Bernstein Report on BioBusiness March 2006:A13-5.

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http://www.i-pwg.org

12.4 ECOG Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.
* As published in Am J Clin Oncol: *Oken 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;5:649-55.* Eastern Cooperative Oncology Group, Robert Comis MD, Group Chair.	

12.5 Common Terminology Criteria for Adverse Events V4.0 (CTCAE)

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for adverse event reporting (http://ctep.cancer.gov/reporting/ctc.html).

12.6 Response Evaluation Criteria in Solid Tumors (RECIST) V1.1 Criteria for Evaluating Response in Solid Tumors

A modification to RECIST version 1.1* will be used in this study for patient management. While either CT or MRI may be used utilized, as per RECIST 1.1, CT is the preferred imaging technique in this study. Details are provided in the Image Acquisition Guidelines..

* As published in the European Journal of Cancer:

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

12.7 List of Abbreviations

Abbreviation/Term	Definition
1L	First line
AE	Adverse event
ADA	Anti-Drug Antibodies
ALT	Alanine aminotransferase
ALK	Anaplastic lymphoma kinase
ANC	Absolute neutrophil count
aPTT	Activated partial thromboplastin time
AUC	Area under curve
AST	Aspartate aminotransferase
β-HCG	Beta-human chorionic gonadotropin
BSC	Best supportive care
CBC	Complete blood count
CI	Confidence interval
CNS	Central nervous system
CR	Complete response
CrCl	Calculated creatinine clearance
CRF	Case report form
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Toxicity Criteria for Adverse Events
DLT	Dose limiting toxicity
DNA	Deoxyribonucleic acid
DMC	Data Monitoring Committee
ECIs	Events of clinical interest
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency
ERC	Ethics review committee
FBR	Future Biomedical Research
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
Hb	Hemoglobin
HBV	Hepatitis B
HCV	Hepatitis C
HIV	Human immunodeficiency virus
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Conference on Harmonization
IHC	Immunohistochemistry
INR	International normalized ratio
irAEs	Immune-related adverse events
IRB	Institutional Review Board
ITT	Intent-to-treat
IV	Intravenous
kg	Kilogram
LDH	Lactate dehydrogenase
mcL	Millimeters
MEL	Melanoma
MG	Milligram
mg/kg	Milligram per kilogram
MRI	Magnetic resonance imaging
MSD	Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.

Abbreviation/Term	Definition
MTD	Maximum tolerated dose
NA or N/A	Not applicable
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NHANES	National Health and Nutrition Examination Survey
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival
OTC	Over-the-counter
PD	Progressive disease
PET	Positron emission tomography
PFS	Progression free survival
PFS2	Next line of therapy PFS2
PGt	Pharmacogenetic
PK	Pharmacokinetic
PK-PD	Pharmacokinetic-Pharmacodynamic
P	Protocol
PRO	Patient reported outcome
PR	Partial response
PT	Prothrombin time
Q2W	Every 2 weeks
Q3W	Every 3 weeks
Q-TWiST	Quality-adjusted Time without Symptoms or Toxicity
RCC	Renal cell carcinoma
RNA	Ribonucleic acid
RECIST	Response Evaluation Criteria in Solid Tumors Version 1.1
RR	Response rate
SAE	Serious adverse events
SAP	Statistical Analysis Plan
SFU	Survival follow-up
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SOC	Standard of care
TIL	Tumor-infiltrating lymphocytes
TKI	Tyrosine kinase inhibitors
TPS	Tumor proportion score
TSH	Thyroid stimulating hormone
TTP	Time to progression
ULN	Upper limit of normal
WHO	World Health Organization
wt	Wild type

13.0 SIGNATURES

13.1 Sponsor's Representative

TYPED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	

13.2 Investigator

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

TYPED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	