Official Protocol Title:	A Randomized, Double-Blind, Phase III Study of Platinum+ Pemetrexed Chemotherapy with or without Pembrolizumab (MK-3475) in First Line Metastatic Non-squamous Non-small Cell Lung Cancer Subjects (KEYNOTE-189)
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TITLE:

A Randomized, Double-Blind, Phase III Study of Platinum+ Pemetrexed Chemotherapy with or without Pembrolizumab (MK-3475) in First Line Metastatic Non-squamous Non-small Cell Lung Cancer Subjects (KEYNOTE-189)

IND NUMBER: 116,833
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SUMMARY OF CHANGES

PRIMARY REASON(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
2.1 4.2.3.1 8.1 8.4.1 8.5.1 8.6.1 8.7 8.8 8.9 8.10	Trial Design Efficacy Endpoints Statistical Analysis Plan Summary Efficacy Endpoints Efficacy Analysis Populations Statistical Methods for Efficacy Analyses Interim Analyses Multiplicity Sample Size and Power Calculations Subgroup Analyses and Effect of Baseline Factors	Timing of interim analysis 1 (IA1) was changed to occur after approximately 370 progression-free survival (PFS) events have been observed. The total type I error allocated to PFS is subject to rollover to overall survival (OS) if the PFS test is positive. The type I error allocated to OS is subject to rollover to PFS if the OS test is positive. The total type I error (from PFS and OS) is subject to rollover to objective response rate (ORR) at IA1 if the PFS and OS tests are both positive. Interim analysis 2 (IA2) will be performed after approximately 468 PFS events have occurred and will evaluate PFS and OS. The final analysis will be performed after approximately 416 deaths have occurred and will evaluate OS.	To provide a more robust analysis of the data, focusing on OS and adjust the alpha spending to most inform the clinical meaningfulness of the data. In addition, subject accrual was greater than originally expected and estimated timing of interim analyses can now be calculated based on actual enrollment (N=616), rather than the planned enrollment (N=570).

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
3.1 3.2 8.4.1 8.6.1.3	Primary Objective(s) & Hypothesis(es) Secondary Objective(s) & Hypothesis(es) Efficacy Endpoints Objective Response Rate and Duration of Response	Promoted OS objective to primary and ORR objective to key secondary.	To provide a more robust analysis of the data, focusing on OS and adjust the alpha spending to most inform the clinical meaningfulness of the data.

ADDITIONAL CHANGE(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
3.0 3.1 3.2 3.3	Objectives Primary Objective(s) & Hypothesis(es) Secondary Objective(s) & Hypothesis(es) Exploratory Objectives	Deleted duplicated objectives and revised wording of remaining objectives for clarity and consistency with current pembrolizumab development program standards.	To remove redundancies.
1.0 2.1 3.2 8.1	Trial Summary Trial Design Secondary Objective(s) & Hypothesis(es) Statistical Analysis Plan Summary	Made the terminology for the chemotherapy regimen consistent throughout the protocol: pemetrexed/platinum	To correct typographical errors and clarify intended meaning.

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
5.2	Trial Treatment(s)	Made typographical corrections and minor administrative edits.	To correct typographical errors and clarify intended meaning.
5.2.1.2	Dose Modification		
5.2.1.2.1	Dose Modification and Toxicity Management Guidelines for Pembrolizumab		
5.5.2	Prohibited Concomitant Medications		
5.8	Subject Withdrawal/ Discontinuation Criteria		
6.1	Initial Treatment Phase		
6.2	Second Course (Retreatment) Phase		
6.3	Crossover Phase		
7.1.2.6.4	Second Course (Retreatment) and Crossover Tumor Imaging		
7.1.3.2.2	Blood Collection for Pemetrexed, Carboplatin, or Cisplatin		
7.1.5.4	Second Course Phase (Retreatment Period)		
7.1.5.5	Crossover for Subjects With Documented Disease Progression Who Received Placebo		
7.1.5.6	Crossover Assessments and Procedures		

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
8.4.1 8.6.1.1 8.6.1.2 8.6.1.3 8.6.3	Efficacy Endpoints Progression-free Survival (PFS) Overall Survival (OS) Objective Response Rate (ORR) and Duration of Response (DOR) Summaries of Demographic and Baseline Characteristics and Other Analysis		
5.2.1.2.1	Dose Modification and Toxicity Management Guidelines for Pembrolizumab	Updated the dose modification and toxicity management guidelines for pembrolizumab to include new information on myocarditis.	To align with the pembrolizumab development program current standards.
6.1 6.2 6.3 7.1.2.6.3 7.1.2.6.4	Initial Treatment Phase Second Course (Retreatment) Phase Crossover Phase End of Treatment and Follow-up of Tumor Imaging Second Course (Retreatment) and Crossover Tumor Imaging	Revised description of imaging at treatment discontinuation and beyond for clarity.	To align with the pembrolizumab development program current standards.
6.1 7.1.3.2	Initial Treatment Phase Pharmacokinetic/Pharmacodynamic Evaluations	Revised details regarding pharmacokinetic and anti-pembrolizumab antibody sample collection and analysis for clarity.	To provide subjects and trial site personnel more accurate information regarding planned PK sample collection and analysis.

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
7.1.4.2 9.3	Blinding/Unblinding Clinical Supplies Disclosure	Specified that if a subject's treatment must be unblinded, the principal investigator, site personnel, and Sponsor personnel will be unblinded in order to provide appropriate medical care.	To clarify expectations regarding an unblinding incident.
2.1 6.1 6.2 6.3 7.1.5.3.3 7.1.5.4 (new)	Trial Design Initial Treatment Phase Second Course (Retreatment) Phase Crossover Phase Survival Follow-up Survival Status (new)	Specified that sites may be required to assess survival status at additional time points during the study.	To clarify survival status reporting requirements.
7.1.5.3.1	Safety Follow-up Visit	Specified that there may be a total of 2 safety follow-up visits for subjects who participate in the Crossover Phase.	To align with the pembrolizumab development program current standards.
8.5.1	Efficacy Analysis Populations	Specified that efficacy analyses may be conducted using the Full Analysis Set (FAS).	To address a situation in which an unexpected number of randomized subjects are not treated.

1.0 TRIAL SUMMARY

Abbreviated Title	Phase III study of Pemetrexed+Platinum with or without Pembrolizumab in first line (1L) metastatic non-squamous NSCLC
Trial Phase	Phase 3
Clinical Indication	Treatment of Non-Small Cell Lung Cancer
Trial Type	Interventional
Type of control	Placebo with Active control
Route of administration	Intravenous
Trial Blinding	Double-blind
Treatment Groups	There are 2 treatment arms: • Pembrolizumab plus pemetrexed and carboplatin or cisplatin • Saline placebo plus pemetrexed and carboplatin or cisplatin
Number of trial subjects	Global Study: Approximately 570 subjects will be enrolled. Extension Study in Japan: Approximately 40 Japanese subjects overall will be enrolled in the global study and the extension study.
Estimated duration of trial	Global Study: The Sponsor estimates that the trial will require approximately 4 years from the time the first subject signs the informed consent until the last subject's last study-related phone call or visit. Extension Study in Japan: The Sponsor estimates that the trial will require approximately an additional 9 months from the time the first subject signs the informed consent until the last subject's last study-related phone call or visit.
Duration of Participation	Each subject will participate in the trial from the time the subject signs the Informed Consent Form (ICF) through the final contact. After a screening phase of up to 28 days, eligible subjects will receive assigned treatment on Day 1 of each 3-week (Q3W) dosing cycle. Treatment with pembrolizumab will continue until 35 treatment administrations of pembrolizumab therapy have been administered, documented disease progression, unacceptable adverse event(s), intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw the subject, subject withdraws consent, pregnancy of the subject, noncompliance with the trial treatment or procedure requirements or administrative reasons. Subjects who experience documented disease progression will have treatment assignment unblinded and be able to continue on open-label pembrolizumab monotherapy in the Crossover Phase. Pembrolizumab treated subjects who have been on therapy for ≥ 6 months and who attain a complete response may consider stopping trial treatment. These subjects, as well as subjects assigned to the pembrolizumab arm who stop trial therapy after 35 treatment administrations for reasons other than disease progression or intolerability, may be eligible for re-treatment with pembrolizumab (Second Course Phase) upon experiencing radiographic disease progression. Participation in the Second Course Phase is at the discretion of the investigator according to the criteria in Section 7.1.5.4. After the end of treatment, each subject will be followed for a minimum of 30 days for adverse event monitoring even if the patient started new antineoplastic treatment (serious adverse events will be collected for up to 90 days following

	cessation of Sponsor's product, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier. Subjects will have post-treatment follow-up for disease status, including radiographic imaging every 12 weeks, until initiating a non-study cancer treatment, experiencing disease progression, death, withdrawing consent, or becoming lost to follow-up.

Randomization Ratio	Randomized 2:1 to either receive pembrolizumab combined with pemetrexed and platinum (investigator's choice of cisplatin or carboplatin), or saline placebo with pemetrexed and platinum (investigator's choice of cisplatin or carboplatin)

A list of abbreviations used in this document can be found in Section 12.4.

2.0 TRIAL DESIGN

2.1 Trial Design

This is a worldwide, randomized, active-controlled, parallel-group, multi-site, double-blind trial of intravenous (IV) pembrolizumab (also known as MK-3475) combined with pemetrexed/platinum chemotherapy versus saline placebo combined with pemetrexed/platinum chemotherapy in subjects with advanced or metastatic nonsquamous non-small cell lung cancer (NSCLC) who have not previously received systemic therapy for advanced disease and in whom EGFR or ALK-directed therapy is not indicated. Approximately 570 subjects will be enrolled in this trial to examine the efficacy of pembrolizumab combined with chemotherapy compared to chemotherapy alone. Subjects will be randomized 2:1 to either receive pembrolizumab 200 mg combined with pemetrexed and platinum (investigator's choice of cisplatin or carboplatin), or saline placebo, pemetrexed and platinum (investigator's choice of cisplatin or carboplatin) as indicated below:

- Arm 1: Pembrolizumab 200 mg + pemetrexed 500 mg/m^2 (with vitamin supplementation) + cisplatin 75 mg/m^2 OR carboplatin AUC 5, all on Day 1 every 3 weeks (Q3W) for 4 cycles followed by pembrolizumab 200 mg + pemetrexed 500 mg/m^2 Q3W until progression.
- Arm 2: Saline placebo + pemetrexed 500 mg/m^2 (with vitamin supplementation) + cisplatin 75 mg/m^2 OR carboplatin AUC 5, all on Day 1 Q3W for 4 cycles followed by saline placebo + pemetrexed 500 mg/m^2 Q3W until progression.

Subjects who received adjuvant or neoadjuvant therapy are permitted onto the study if the therapy was completed at least 12 months prior to the development of metastatic disease.

Subjects will be stratified by smoking status (never vs former/current), cisplatin vs carboplatin, and programmed cell death ligand-1 (PD-L1) status (Tumor Proportion Score [TPS] ≥1% vs <1%) prior to randomization. PD-L1 inevaluable subjects will be included with the TPS <1% group.

Subjects will be evaluated at 6 weeks (42 ± 7 days) and 12 weeks (84 ± 7 days) and then every 9 weeks (63 ± 7 days) with radiographic imaging to assess response to treatment for the first 48 weeks and every 12 weeks (84 ± 7 days) subsequently; treatment-based decisions should be based on the immune-related RECIST criteria (irRECIST) (details are provided in the Procedure Manual). All imaging obtained on study will be submitted without indication

of treatment assignment to a central imaging review vendor, ie, blinded independent central review (BICR), who will assess the images using Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) for determination of progression-free survival (PFS) and objective response rate (ORR). 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 or saline placebo 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.

Treatment with pemetrexed will continue until 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.

At the time of documented disease progression as confirmed by BICR using RECIST 1.1, subjects will have treatment assignment unblinded and may be able to continue therapy in the Crossover Phase as indicated below until subsequent documented 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:

1. Subjects who had received saline placebo in combination with chemotherapy will be able to receive open-label pembrolizumab monotherapy for a total of 35 treatments.
2. Subjects who had received pembrolizumab in combination with chemotherapy, but are deemed to be benefiting clinically despite progression, will be able to receive open-label pembrolizumab monotherapy to complete a total of 35 treatments.

Subjects who attain a confirmed complete response (CR) per irRECIST may consider stopping trial treatment. These subjects, as well as subjects assigned to the pembrolizumab arm who stop trial therapy after 35 treatment administrations for reasons other than disease progression or intolerability, may be eligible for the Second Course Phase. The Second Course Phase is re-treatment with open-label pembrolizumab monotherapy after radiographic disease progression and participation is at the discretion of the investigator according to defined criteria in Section 7.1.5. Response or progression in the Second Course Phase will not count towards the PFS and ORR 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) will be collected for up to 90 days after the end of treatment or 30 days following cessation of treatment if the subject initiates new cancer therapy, whichever is earlier. Subjects will have post-treatment follow-up for disease status, until initiating a non-study cancer treatment, experiencing disease progression, death, withdrawing consent, or becoming lost to follow-up.

The Sponsor may request survival status to be assessed at additional time points and entered into the database during the course of the trial. For example, survival status may be requested prior to, but not limited to, an external Data Monitoring Committee (eDMC) review.

The primary endpoints of the trial are PFS (BICR/RECIST 1.1) and overall survival (OS). The key secondary endpoint is ORR (BICR/RECIST 1.1); other endpoints include duration of response (DOR) (BICR/RECIST 1.1) and safety as assessed by a variety of AE parameters. Exploratory analyses include PFS, OS, and ORR by PD-L1 expression levels and PFS, ORR, and DOR by investigator-assessed RECIST 1.1 and irRECIST. Drug-drug interaction studies and quality of life assessments are further exploratory endpoints.

Participation in this trial will be dependent upon supplying tumor tissue from locations not radiated prior to biopsy; formalin-fixed specimens used to confirm diagnosis or collected after the subject has been diagnosed with metastatic disease will be preferred for determination of PD-L1 status prior to randomization. Biopsies obtained prior to receipt of adjuvant/neoadjuvant chemotherapy will be permitted if recent biopsy is not feasible. Subjects who received adjuvant/neoadjuvant therapy are permitted onto the trial as long as therapy was completed at least 12 months prior to the diagnosis of metastatic disease. Subjects whose submitted tissue is inevaluable for PD-L1 status can still be eligible to participate in the study.

The specimen will be evaluated at a central laboratory facility for expression status of PD-L1 in a prospective manner to enable stratification. In terms of stratification, PD-L1 non-evaluable subjects will be grouped with the TPS <1% group.

Two interim analyses will be conducted during the course of the trial with review by the eDMC. The first interim analysis (IA1) will be performed after approximately 370 PFS events have been observed. The second interim analysis (IA2) will be performed after approximately 468 PFS events have been observed. The final analysis (FA) will be performed after approximately 416 deaths have been observed. In addition, the trial may be stopped early at the recommendation of the eDMC if the risk/benefit ratio to the trial population as a whole is unacceptable. Details are described in Section 8.0 Statistical Analysis Plan.

Extension Study

Approximately 40 Japanese subjects overall will be enrolled in the global study and the extension study. After the enrollment period of the global study is closed, subjects from Japan will continue to be enrolled in an extension study mainly to collect additional Japanese safety data. The extension study will be identical to the global study (eg, inclusion and exclusion criteria, study endpoints, primary and secondary objectives, study procedures), with the exception of an additional Statistical Analysis Plan (SAP) for Japanese subjects. Details of the analysis will be provided in a separate Japan-specific SAP document.

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

2.2 Trial Diagram

The trial design is depicted in Figure 1.

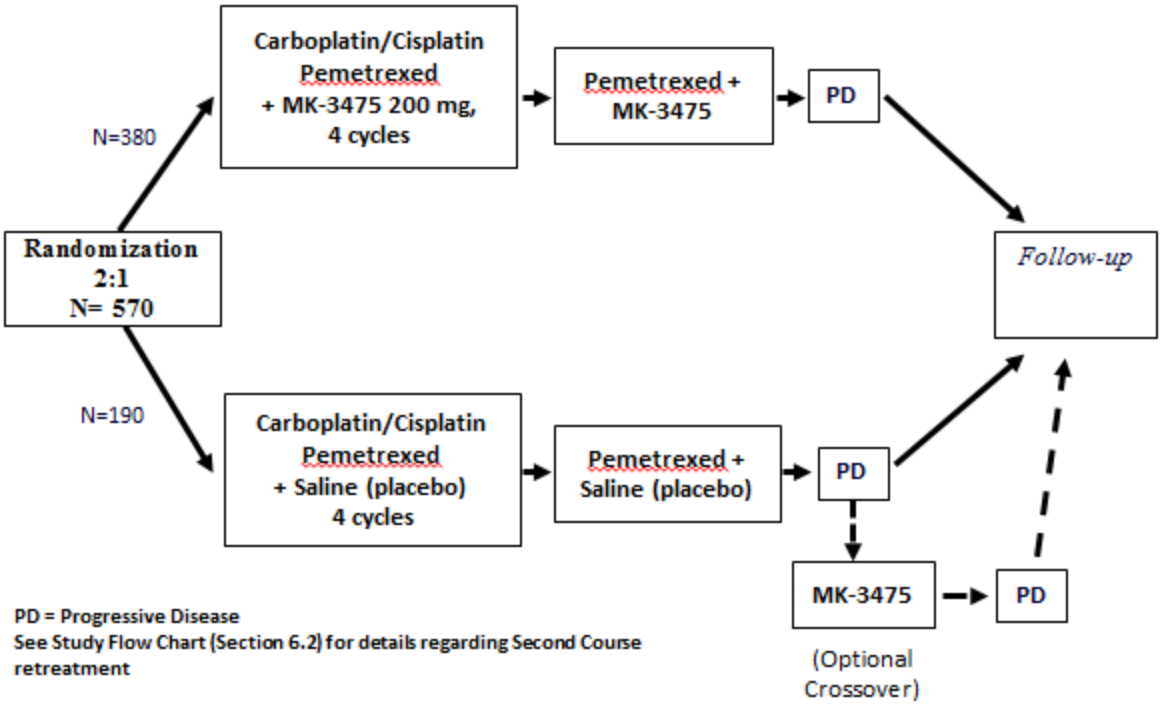

Figure 1 Study Schema

3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

Pembrolizumab in combination with chemotherapy will be compared with saline placebo in combination with chemotherapy in subjects with advanced or metastatic nonsquamous, non-small cell lung cancer (NSCLC) who have not previously received systemic therapy based on the following primary, secondary, and exploratory objectives:

3.1 Primary Objective(s) & Hypothesis(es)

1. To evaluate the antitumor activity of pembrolizumab in combination with chemotherapy compared with saline placebo in combination with chemotherapy using PFS per RECIST 1.1 as assessed by BICR of imaging.

   Hypothesis: Pembrolizumab in combination with chemotherapy prolongs PFS (BICR/RECIST 1.1) compared to saline placebo in combination with chemotherapy.

2. To evaluate the antitumor activity of pembrolizumab in combination with chemotherapy compared with saline placebo in combination with chemotherapy using OS.

Hypothesis: Pembrolizumab in combination with chemotherapy prolongs OS compared to saline placebo in combination with chemotherapy.

3.2 Secondary Objective(s) & Hypothesis(es)

1. To evaluate the antitumor activity of pembrolizumab in combination with chemotherapy compared with saline placebo in combination with chemotherapy using ORR per RECIST 1.1 as assessed by BICR.

   Hypothesis: Pembrolizumab in combination with chemotherapy improves ORR (BICR/RECIST 1.1) compared with saline placebo in combination with chemotherapy.
2. To evaluate the antitumor activity of pembrolizumab in combination with chemotherapy compared with saline placebo in combination with chemotherapy using DOR per RECIST 1.1 as assessed by BICR.
3. To evaluate the safety and tolerability profile of pembrolizumab in combination with pemetrexed/platinum chemotherapy.

3.3 Exploratory Objectives

1. To evaluate the effect of PD-L1 expression levels on the efficacy endpoints of PFS, OS, and ORR.
2. To evaluate the antitumor activity of pembrolizumab in combination with chemotherapy compared with saline placebo in combination with chemotherapy using PFS, ORR, and DOR assessed by the investigator using RECIST 1.1.
3. To evaluate the antitumor activity of pembrolizumab in combination with chemotherapy compared with saline placebo in combination with chemotherapy using PFS, ORR, and DOR per investigator-assessed irRECIST response criteria.
4. To investigate the relationship between pembrolizumab treatment and biomarkers predicting response (eg, PD-L1, genetic variation, serum sPD-L1) utilizing newly obtained or archival FFPE tumor tissue and blood, including serum and plasma.
5. To evaluate changes in health-related quality-of-life assessments from baseline in the biomarker-positive strata and in the overall study population using the EORTC QLQ-C30 and EORTC QLQ-LC13.
6. To characterize utilities in subjects treated with pembrolizumab in combination with chemotherapy compared with saline placebo in combination with chemotherapy using the EuroQoL(EQ)-5D.
7. To characterize the pharmacokinetic characteristics of pemetrexed/platinum treatment and pembrolizumab.

8. To explore the relationship between genomic variation and response to the treatment(s) administered. Variation across the human genome (germline and tumor) will be analyzed for association with clinical data collected in this study.
9. To evaluate PFS and OS following crossover to pembrolizumab in subjects initially treated with saline placebo in combination with chemotherapy.

4.0 BACKGROUND & RATIONALE

4.1 Background

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

4.1.1 Pharmaceutical and Therapeutic Background

The 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] [4] [5] [6] [7] [8]. In particular, the presence of CD8+ T -cells and the ratio of CD8+ effector T -cells / FoxP3+ regulatory T-cells seems to correlate with improved prognosis and long -term survival in solid malignancies such as ovarian, colorectal and pancreatic cancer, hepatocellular carcinoma, malignant melanoma and renal cell carcinoma (RCC). TILs can be expanded ex vivo and re-infused, inducing durable objective tumor responses in cancers such as melanoma [9] [10].

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) [11] [12]. 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 [13] [14]. 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 [15] [16]. 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 [14] [17] [18] [19]. 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 [17]. 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 17 [20], pancreatic carcinoma [21], hepatocellular carcinoma [22], and ovarian carcinoma [23]. Furthermore, PD-1 has been suggested to regulate tumor-specific T-cell expansion in subjects with melanoma [24].

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 2/3 trial of pembrolizumab vs docetaxel in previously treated subjects with advanced or metastatic NSCLC.

4.1.2 Pre-clinical and Clinical Trials

Anti-mouse PD-1 or anti-mouse PD-L1 antibodies have demonstrated anti-tumor responses as a mono-therapy in models of squamous cell carcinoma, pancreatic carcinoma, melanoma and colorectal carcinoma. Blockade of the PD-1 pathway effectively promoted CD8+ T-cell infiltration into the tumor and the presence of IFN-gamma, granzyme B and perforin, indicating that the mechanism of action involved local infiltration and activation of effector T-cell function in vivo [23] [25] [26] [27] [28] [29]. In addition, the combination of gemcitabine and anti-PD-L1 mAb demonstrated synergy in the rejection of pancreatic mouse tumors [23]. 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 and NSCLC. In an ipilimumab-refractory cohort of melanoma patients who received pembrolizumab 10 mg/kg or 2 mg/kg IV Q3W, the ORR was 24% (95% CI 15-34) in the 2 mg/kg arm, consisting of 1 CR and 20 PRs. Among the 21 subjects with an objective response, 3 (14%) had PD 2.8, 2.9, and 8.2 months after initial response. The remaining 18 subjects (86%) had ongoing responses with durations ranging from 1.4+ to 8.5+ months, which included 8 subjects with ongoing responses of 6 months or longer. Furthermore, the toxicity profile was manageable with the majority of the toxicities at Grade 1 or 2 [30].

In the same open-label multi-cohort Phase 1 trial (KEYNOTE-001), a total of 495 NSCLC subjects were treated with at least 1 dose of pembrolizumab. The ORR was 19.4% (18.0% in the 394 previously treated subjects and 24.8% in the 101 previously untreated subjects). The response rate 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 [TPS] ≥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 TPS 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 [31].

4.1.3 Ongoing Clinical Trials

A number of clinical trials are exploring the value of pembrolizumab monotherapy compared to standard chemotherapy in a PD-L1-enriched population, both as second-line therapy (KEYNOTE-010) and first-line therapy (KEYNOTE-024 and KEYNOTE-042) with results expected in 2015-2016. Chemotherapy combinations with pembrolizumab are being explored in a Phase1B/2 study (KEYNOTE-021); preliminary data presented at ASCO 2015 suggest a manageable toxicity profile and an encouraging response rate of 58% with the combination of pembrolizumab and carboplatin-pemetrexed as first-line therapy.

4.1.4 Information on Other Trial-related Therapy

Platinum doublet chemotherapy is the standard of care for the treatment of patients with good performance status (ECOG 0 or 1), advanced or metastatic, previously untreated NSCLC in whom EGFR or ALK-directed therapy is not indicated. Treatments include cisplatin or carboplatin in combination with either paclitaxel, gemcitabine, pemetrexed or docetaxel [32]. Multiple Phase 3 studies have demonstrated similar efficacy for most platinum doublets in NSCLC patients; study ECOG 1594 being the most cited [33].

A meta-analysis of randomized controlled clinical trials compared chemotherapy regimens containing either cisplatin or carboplatin in combination with third generation antineoplastic agents including docetaxel, paclitaxel, and gemcitabine. Cisplatin containing regimens were associated with a median survival of 9.1 months and a 1-year survival probability of 37%, while carboplatin containing regimens were associated with a median survival of 8.4 months and a 1-year survival probability of 34%. The risk of death was higher with carboplatin compared with cisplatin, although the difference was not statistically significant (HR 1.07, 95% CI 0.99-1.15, p=0.100). These data support the interchangeable use of carboplatin or cisplatin in combination with standard of care antineoplastic agents [34].

In a non-inferiority, Phase 3 trial, overall survival in 1725 subjects with previously untreated NSCLC was found to be non-inferior after treatment with cisplatin and pemetrexed compared to cisplatin combined with gemcitabine (median survival 10.3 months vs 10.3 months; HR 0.94; 95% CI 0.84–1.05%) [35]. However, in a planned subgroup analysis, cisplatin and pemetrexed was found to be superior in subjects with nonsquamous NSCLC (n = 1000; HR 0.81; 95% CI, 0.7 – 0.94; p = 0.005). In contrast, subjects with squamous cell histology did better with cisplatin and gemcitabine (n = 473; 10.8 months versus 9.4 months, respectively, p = 0.05). Pemetrexed and platinum therapy has become a significant treatment of choice for advanced nonsquamous NSCLC. Continuation of pemetrexed after initial four cycles of pemetrexed cisplatin demonstrated a survival benefit in a randomized double-blind, placebo-controlled study: median overall survival 13.9 months (CI 12.8-16.0) for pemetrexed compared to 11.0 months (CI 10.0-12.5) for placebo and a hazard ratio of 0.78 (CI 0.64-0.96) [36].

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

Lung cancer accounted for an estimated 13% of total cancer diagnoses, representing 1.8 million new cases in 2012. Mortality from lung cancer in 2012 amounted to 1.6 million

deaths globally: the leading cause of cancer death in men and the second leading cause in women [37]. NSCLC accounts for approximately 85% of all lung cancer cases, with the majority being nonsquamous.

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% [38] 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 conferring the greatest advances in overall survival gains. As noted in Section 4.1.4, platinum and pemetrexed therapy has become a relative standard option for nonsquamous NSCLC.

Molecular profiling has, however, established a definite role for EGFR and ALK directed therapy in a small subset of NSCLC patients. The EGFR tyrosine kinase inhibitors gefitinib, erlotinib and afatinib have demonstrated marked superiority over chemotherapy in patients with activating EGFR mutations. In addition, agents that overcome resistance to initial therapy are also in development. Similarly, ALK inhibitors crizotinib and ceritinib have shown significant activity in ALK-rearranged NSCLC with more agents in development. Interestingly, the ALK inhibitors are also active in a rare subgroup of ROS-1 rearranged NSCLC patients.

This study will, therefore, be restricted to nonsquamous NSCLC subjects in whom EGFR or ALK directed therapy is not indicated. Importantly, subjects will not be selected by PD-L1 expression status, although this is a stratification factor.

4.2.2 Rationale for Dose Selection/Regimen/Modification

4.2.2.1 Rationale for Pembrolizumab Dose

The dose of pembrolizumab planned to be studied in this trial is 200 mg Q3W. The dose recently approved in the United States and several other countries for treatment of melanoma subjects is 2 mg/kg Q3W. Information on the rationale for selecting 200 mg Q3W is summarized below.

KEYNOTE-001, an open-label Phase 1 study is being conducted to evaluate the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD), and anti-tumor 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) and dose expansion cohorts evaluated 2 mg/kg Q3W and 10 mg/kg Q3W in subjects with advanced solid tumors. All dose levels were well tolerated and no dose-limiting toxicities were observed. This first-in-human study of pembrolizumab showed evidence of target engagement and objective evidence of tumor size reduction at all dose levels. No maximum tolerated dose (MTD) has been identified. In addition, two randomized cohort evaluations of melanoma subjects receiving pembrolizumab at a dose of 2 mg/kg versus 10 mg/kg Q3W have been completed, and one randomized cohort evaluating 10 mg/kg Q3W versus

10 mg/kg Q2W has also been completed. The clinical efficacy and safety data demonstrate a lack of important differences in efficacy or safety profile across doses.

An integrated body of evidence suggests that 200 mg every 3 weeks (Q3W) is expected to provide similar response to 2 mg/kg Q3W, 10 mg/kg Q3W and 10 mg/kg Q2W. Previously, a flat pembrolizumab exposure-response relationship for efficacy and safety has been found in subjects with melanoma in the range of doses between 2 mg/kg and 10 mg/kg. Exposures for 200 mg Q3W are expected to lie within this range and will be close to those obtained with 2 mg/kg Q3W dose.

A population pharmacokinetic (PK) model, which characterized the influence of body weight and other patient covariates on exposure, has been developed. The PK profile of pembrolizumab is consistent with that of other humanized monoclonal antibodies, which typically have a low clearance and a limited volume of distribution. The distribution of exposures from the 200 mg fixed dose are predicted to considerably overlap those obtained with the 2 mg/kg dose and importantly will maintain individual patient exposures within the exposure range established in melanoma as associated with maximal clinical response. Pharmacokinetic properties of pembrolizumab, and specifically the weight-dependency in clearance and volume of distribution are consistent with no meaningful advantage to weight-based dosing relative to fixed dosing.

In translating to other tumor indications, similarly flat exposure-response relationships for efficacy and safety as observed in subjects with melanoma can be expected, as the anti-tumor effect of pembrolizumab is driven through immune system activation rather than through a direct interaction with tumor cells, rendering it independent of the specific tumor type. In addition, available PK results in subjects with melanoma, NSCLC, and other tumor types support a lack of meaningful difference in pharmacokinetic exposures obtained at tested doses among tumor types. Thus, the 200 mg Q3W fixed-dose regimen is considered an appropriate fixed dose for other tumor indications as well.

A fixed dose regimen will simplify the dosing regimen to be more convenient for physicians and to reduce potential for dosing errors. A fixed dosing scheme will also reduce complexity in the logistical chain at treatment facilities and reduce wastage. The existing data suggest 200 mg Q3W as the appropriate dose for pembrolizumab.

4.2.2.2 Rationale for the Use of Placebo

The use of saline placebo in combination with standard chemotherapy will ensure the objectivity of investigator-assessed progression as well as any decisions to interrupt/discontinue therapy. Since randomization and placebo use can be a perceived barrier to subject enrollment, a 2:1 randomization will be used to enhance subject accrual.

4.2.3 Rationale for Endpoints

4.2.3.1 Efficacy Endpoints

Primary

PFS is an acceptable measure of clinical benefit for a randomized Phase 3 trial that demonstrates superiority of a new antineoplastic therapy, especially if the magnitude of effect is large and the therapy has an acceptable risk-benefit profile. Furthermore, it is an endorsed regulatory endpoint for first-line NSCLC trials with recent FDA and EMA approvals including the EGFR inhibitors afatinib and erlotinib. PFS will be assessed per RECIST 1.1 by central imaging vendor that will be blinded to the treatment assignment to minimize any bias in the response assessments. In addition, final determination of radiologic progressive disease (PD) will be based on the central imaging vendor assessment of progression, rather than local site investigator/radiology assessment. Expedited assessment by the central imaging vendor in instances of suspected radiological progression identified at the site (verification of PD) will be communicated to the study team. Approval of nivolumab in the second line setting as well as multiple clinical trial opportunities will make subject crossover to a PD-1/PD-L1 agent from the control group almost certain and negate any ability to measure overall survival reliably.

OS has been recognized as the gold standard for the demonstration of superiority of a new antineoplastic therapy in randomized clinical studies.

Secondary

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

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

4.2.3.2 Immune-related RECIST (irRECIST)

RECIST 1.1 will be adapted to account for the unique tumor response characteristics seen with treatment of pembrolizumab. Immunotherapeutic agents such as pembrolizumab may produce antitumor effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such an approach may extend beyond the typical time course of responses seem with cytotoxic agents, and can manifest a clinical response after an initial increase in tumor burden or even the appearance of new lesions.

Standard RECIST 1.1 may, thus, not provide a complete response assessment of immunotherapeutic agents such as pembrolizumab. Based on an analysis of patients with melanoma enrolled in KEYNOTE-001, 7% of evaluable subjects experienced delayed or early tumor pseudo-progression. Of note, subjects who had progressive disease by RECIST 1.1 but not by immune-related Response Criteria had longer OS than subjects with progressive disease by both criteria. Additionally, the data suggest that RECIST 1.1 may underestimate the benefit of pembrolizumab in approximately 15% of subjects. These findings support the need to apply a modification to RECIST 1.1 that takes into account the unique patterns of atypical response in immunotherapy and enable treatment beyond initial radiographic progression. However, it is not clear whether the same pattern will be observed

in combination with chemotherapy, hence RECIST 1.1 will remain the primary assessment method.

Immune-related RECIST (irRECIST) is RECIST 1.1 adapted to account for the unique tumor response seen with immune-therapeutics as described in [39]. The assessment of unidimensional target lesions and response categories per irRECIST are identical to RECIST 1.1. However, Merck has implemented an adaptation related to new lesions, non-target and tumor burden assessment in order to confirm radiographic progression. irRECIST will be used by local site investigators to assess tumor response and progression, and make treatment decisions.

4.2.3.3 Rationale for Safety Endpoints

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

4.2.3.4 Patient Reported Outcomes

4.2.3.4.1 EORTC QLQ-C30 and EORTC QLQ-LC13

The EORTC QLQ-C30 was developed to assess the quality of life of cancer subjects and is the most widely used cancer-specific HRQoL instrument. It contains 30 items and measures five functional dimensions (physical, role, emotional, cognitive, and social), three symptom items (fatigue, nausea/vomiting, and pain), six single items (dyspnea, sleep disturbance, appetite loss, constipation, diarrhea, and financial impact) and global health and quality of life. The global health and quality of life scale uses a 7 point scale scoring with anchors (1=very poor and 7=excellent); the other items are scored on a 4 point scale (1=not at all, 2=a little, 3= quite a bit, 4=very much).

The EORTC QLQ-LC13, a supplemental lung cancer-specific module used in combination with QLQ-C30, comprises multi-item and single-item measures of lung cancer-associated symptoms (cough, hemoptysis, dyspnea, and site specific pain) and treatment-related symptoms (sore mouth, dysphagia, peripheral neuropathy and alopecia) [40]. It is scored on a 4 point scale (1=not at all, 2=a little, 3=quite a bit, 4=very much) and has been translated and validated into more than 60 languages.

The EORTC QLQ-C30 and QLQ-LC13 are the most frequently utilized and reported patient-reported outcome measures in lung cancer clinical trials. The reliability, validity and practicality of these instruments have been reported [40] [41].

4.2.3.4.2 EuroQoL (EQ)-5D

The EuroQol-5D (EQ-5D) is a standardized instrument for use as a measure of health outcome. The EQ-5D will provide data for use in economic models and analyses including developing health utilities or QALYs. The five health state dimensions in this instrument include the following: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension is rated on a three point scale from 1 (extreme problem)

to 3 (no problem). The EQ-5D also includes a graded (0 to 100) vertical visual analog scale on which the subject rates his or her general state of health at the time of the assessment. The EQ-5D will always be completed by subjects first before completing the EORTC QLQ-C30 and EORTC QLQ-LC13.

4.2.3.5 Pharmacokinetic Endpoints

Blood samples will be obtained to measure pharmacokinetics (PK) of pembrolizumab, pemetrexed and carboplatin (or cisplatin).

The pembrolizumab serum maximum concentration (C_{max}) and minimum concentration (C_{trough}) at planned visits and times will be summarized. Pharmacokinetic data will also be analyzed using nonlinear mixed effects modeling. Based on PK data obtained in this study as well as PK data obtained from other studies, a population PK analysis will be performed to characterize pharmacokinetic parameters (Clearance (CL), Volume of distribution (V)) and evaluate the effect of extrinsic and intrinsic factors to support proposed dosing regimen. Pharmacokinetic data will also be used to explore the exposure-response relationships for pembrolizumab antitumor activity/efficacy as well as safety in the proposed patient population, if feasible. The results of these analyses, if performed, will be reported separately.

To estimate the effect of pembrolizumab on the pharmacokinetics of pemetrexed and carboplatin (or cisplatin), pharmacokinetic studies will be conducted in a subset of research participants enrolled on this protocol. See Section 7.1.3.2 for additional details.

4.2.3.6 Planned Exploratory Biomarker Research

Planned Genetic Analysis

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. This research contributes to understanding genetic determinants of efficacy and safety associated with the treatments in this study.

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 & 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.

4.2.3.7 Future Biomedical Research

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

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. 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 informational material for institutional review boards/ethics committees (IRBs/ERCs) and investigational site staff is provided in Section 12.3.

4.3 Benefit/Risk

Details regarding specific benefits and risks for subjects participating in this clinical trial may be found in the accompanying 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.

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

Male/Female subjects with nonsquamous NSCLC who have not received prior systemic chemotherapy treatment for their advanced or metastatic NSCLC, are at least 18 years of age and in whom EGFR or ALK-directed therapy is not indicated will be enrolled in this trial.

5.1.2 Subject Inclusion Criteria

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

1. Have a histologically-confirmed or cytologically confirmed diagnosis of stage IV (M1a or M1b- AJCC 7th edition) nonsquamous NSCLC.
2. Have confirmation that EGFR or ALK-directed therapy is not indicated (documentation of absence of tumor activating EGFR mutations AND absence of ALK gene rearrangements OR presence of a K-Ras mutation).
3. Have measurable disease based on RECIST 1.1 as determined by the local site investigator/radiology assessment. Target lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions.
4. Have not received prior systemic treatment for their advanced/metastatic NSCLC. Subjects who received adjuvant or neoadjuvant therapy are eligible if the adjuvant/neoadjuvant therapy was completed at least 12 months prior to the development of metastatic disease.
5. Have provided tumor tissue from locations not radiated prior to biopsy; formalin-fixed specimens after the subject has been diagnosed with metastatic disease will be preferred for determination of PD-L1 status prior to randomization. Biopsies obtained

prior to receipt of adjuvant/neoadjuvant chemotherapy will be permitted if recent biopsy is not feasible.

6. Be ≥18 years of age on day of signing informed consent.
7. Have a life expectancy of at least 3 months.
8. Have a performance status of 0 or 1 on the Eastern Cooperative Oncology Group (ECOG) Performance Status.
9. Have adequate organ function as indicated by the following laboratory values [Table 1]:

Table 1 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1,500 /mcL
Platelets	≥100,000 / mcL
Hemoglobin	≥9.0 g/dL or ≥5.6 mmol/L– 4 weeks without transfusions
Renal	
calculated creatinine clearance (CrCl)[a]	≥50 mL/min
Hepatic	
Serum total bilirubin	≤1.5xULN OR Direct bilirubin ≤ULN for subjects with total bilirubin levels >1.5xULN
AST (SGOT) and ALT (SGPT)	≤2.5xULN OR ≤5xULN for subjects with liver metastases
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT) Activated Partial Thromboplastin Time (aPTT) or Partial Thromboplastin Time (PTT)	≤1.5 X ULN unless the subject is receiving anticoagulant therapy ≤1.5 X ULN unless the subject is receiving anticoagulant therapy
[a.] Creatinine Clearance should be calculated using the Cockcroft-Gault Method: Refer to Appendix 12.5 for appropriate calculation	

10. If female of childbearing potential (Section 5.7.2), have a negative urine or serum pregnancy test within 72 hours prior to receiving the first dose of study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
11. If female of childbearing potential (Section 5.7.2), be willing to use an adequate method of contraception as outlined in Section 5.7.2-Contraception, for the course of the study through 120 days after the last dose of study medication or through 180 days after last dose of chemotherapeutic agents as specified in the protocol.

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

12. If male subject with a female partner(s) of child-bearing potential, must agree to use an adequate method of contraception as outlined in Section 5.7.2-Contraception, starting with the first dose of study therapy through 120 days after the last dose of

study therapy or through 180 days after last dose of chemotherapeutic agents as specified in the protocol. Males with pregnant partners must agree to use a condom; no additional method of contraception is required for the pregnant partner.

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

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

5.1.3 Subject Exclusion Criteria

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

1. Has predominantly squamous cell histology NSCLC. Mixed tumors will be categorized by the predominant cell type; if small cell elements are present, the subject is ineligible.
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 prior to administration of pembrolizumab.
3. Before the first dose of trial treatment:
   a) Has received prior systemic cytotoxic chemotherapy for metastatic disease
   b) Has received antineoplastic biological therapy (e.g., erlotinib, crizotinib, cetuximab) for metastatic disease
   c) Had major surgery (<3 weeks prior to first dose)
4. Received radiation therapy to the lung that is > 30 Gy within 6 months of the first dose of trial treatment.
5. Completed palliative radiotherapy within 7 days of the first dose of trial treatment.
6. Is expected to require any other form of antineoplastic therapy while on study.
7. Has received a live-virus vaccination within 30 days of planned treatment start. Seasonal flu vaccines that do not contain live virus are permitted.
8. Has clinically active diverticulitis, intra-abdominal abscess, GI obstruction, peritoneal carcinomatosis.
9. Has a known history of prior malignancy except if the subject has undergone potentially curative therapy with no evidence of that disease recurrence for 5 years since initiation of that therapy.

   Note: The time requirement for no evidence of disease for 5 years does not apply to the NSCLC tumor for which a subject is enrolled in the study. The time requirement also does not apply to subjects who underwent successful definitive resection of basal cell carcinoma of the skin, superficial bladder cancer, squamous cell carcinoma of the skin, in situ cervical cancer, or other in situ cancers.

10. Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are clinically stable for at least 2 weeks and, have no evidence of new or enlarging brain metastases and also are off steroids 3 days prior to dosing with study medication. Stable brain metastases by this definition should be established prior to the first dose of study medication. Subjects with known untreated, asymptomatic brain metastases (ie, no neurological symptoms, no requirements for corticosteroids, no or minimal surrounding edema, and no lesion >1.5 cm) may participate but will require regular imaging of the brain as a site of disease.
11. Previously had a severe hypersensitivity reaction to treatment with another mAb.
12. Has a known sensitivity to any component of cisplatin, carboplatin or pemetrexed
13. Has active autoimmune disease that has required systemic treatment in past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.
14. Is on chronic systemic steroids. Subjects with asthma that require intermittent use of bronchodilators, inhaled steroids, or local steroid injections would not be excluded from the study.
15. Is unable to interrupt aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs), other than an aspirin dose ≤ 1.3 g per day, for a 5-day period (8-day period for long-acting agents, such as piroxicam).
16. Is unable or unwilling to take folic acid or vitamin B_{12} supplementation.
17. Had prior treatment with any other anti-PD-1, or PD-L1 or PD-L2 agent or an antibody targeting other immuno-regulatory receptors or mechanisms. Has participated in any other MK-3475 trial and has been treated with MK-3475.

    Examples of such antibodies include (but are not limited to) antibodies against IDO, PD-L1, IL-2R, GITR
18. Has an active infection requiring therapy.
19. Has known history of Human Immunodeficiency Virus (HIV) (known HIV 1/2 antibodies positive).
20. Has known active Hepatitis B or C. Active Hepatitis B is defined as a known positive HBsAg result. Active Hepatitis C is defined by a known positive Hep C Ab result and known quantitative HCV RNA results greater than the lower limits of detection of the assay.
21. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the subject's participation for the full duration of the study, or is not in the best interest of the subject to participate, in the opinion of the treating Investigator.
22. Has known psychiatric or substance abuse disorder that would interfere with cooperation with the requirements of the trial.

23. Is, at the time of signing informed consent, a known regular user of any illicit drugs or had a recent history (within the last year) of substance abuse (including alcohol).
24. Has symptomatic ascites or pleural effusion. A subject who is clinically stable following treatment for these conditions (including therapeutic thoraco- or paracentesis) is eligible.
25. Has a history of (non-infectious) pneumonitis that required steroids or current pneumonitis.
26. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the study.

5.2 Trial Treatment(s)

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

Table 2 Trial Treatment

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/ Treatment Period	Use
Pembrolizumab[1]	200 mg	Q3W	IV infusion	Day 1 of each 21 day cycle	Experimental
Normal saline[1]	N/A	Q3W	IV infusion	Day 1 of each 21 day cycle	Placebo
Cisplatin	75 mg/m ^{2}	Q3W	IV infusion	Day 1 of each 21 day cycle for 4 cycles	Treatment of cancer (comparator)
Carboplatin	AUC 5	Q3W	IV infusion	Day 1 of each 21 day cycle for 4 cycles	Treatment of cancer (comparator)
Pemetrexed	500 mg/m ^{2}	Q3W	IV infusion	Day 1 of each 21 day cycle	Treatment of cancer (comparator)
[1] Pembrolizumab/placebo to be administered prior to chemotherapy.					

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

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)

Pembrolizumab: the dose amount required to prepare the pembrolizumab infusion solution will be based on a fixed dose of 200 mg. Details on preparation and administration of pembrolizumab are provided in the Pharmacy Manual.

Concomitant standard chemotherapeutic agents will be prepared and administered as per the approved product label at the doses indicated below:

- **Pemetrexed:** 500mg/m^2
- **Cisplatin:** 75mg/m^2
- **Carboplatin:** AUC 5 (using Calvert formula). Carboplatin dose not to exceed 750mg

  Calvert Formula

  Total Dose (mg) = (target AUC) x (CrCl + 25)

  The estimated CrCl used in the Calvert formula should not exceed 125 mL/min

  Maximum carboplatin dose (mg) = target AUC 5 (mg•min/mL) x (125 + 25) = 5 x 150 mL/min = 750 mg

5.2.1.2 Dose Modification

If appropriate, the Investigator may attribute each toxicity event to cisplatin/carboplatin, pemetrexed or pembrolizumab alone or to the combination and use a stepwise dose modification according to [Table 3] to [Table 7]. Dose modifications must be based on the maximum toxicity experienced during a cycle. Toxicity needs to resolve to Grade ≤1 or baseline prior to resuming subsequent cycle. For individual subjects requiring a dose modification, treatment for each new cycle may be delayed if the scheduled off-drug periods are not adequate to allow for recovery to Grade ≤1 or the baseline status of the subject.

Pembrolizumab dose reductions are not permitted. Pembrolizumab treatment may be interrupted or discontinued due to toxicity. If a dose reduction for toxicity occurs with any agent, the dose may not be re-escalated. Subjects can have a maximum of 2 dose modifications (if applicable) to each of the components of study therapy throughout the course of the study for toxicities. If a subject experiences several toxicities and there are conflicting recommendations, the most conservative dose adjustment recommended should be followed (dose reduction appropriate to the most severe toxicity). Subjects who require a 3rd dose modification to any particular component will have that agent discontinued.

Reduction of one chemotherapy agent and not the other agent is appropriate if, in the opinion of the Investigator, the toxicity is clearly related to one of the treatments. If, in the opinion of the Investigator, the toxicity is related to the combination of both chemotherapy agents, both drugs should be reduced according to recommended dose modifications. If the toxicity is related to the combination of three agents, all three agents should be reduced (if applicable), interrupted or discontinued according to the recommended dose modifications. Subjects may have chemotherapy discontinued and continue on pembrolizumab/saline placebo alone.

Similarly subjects may discontinue pembrolizumab/saline placebo and continue on chemotherapy alone if appropriate.

Chemotherapy may be interrupted for a maximum of 6 weeks from last dose; pembrolizumab may be interrupted for a maximum of 12 weeks from last dose.

The Common Terminology Criteria for Adverse Events version 4.0 (CTCAE 4.0) must be used to grade the severity of adverse events. All dose modifications should be based on the AE requiring the greatest dose modification. Dose modifications are detailed in [Table 3] through [Table 7].

Table 3 Dose Modifications for Trial Medications

	Dose Level 0	**Dose Level -1**	**Dose Level -2**	**Dose Level -3**
Cisplatin	75 mg/m^2	56 mg/ m^2	38 mg/ m^2	Discontinue
Carboplatin	AUC 5 Maximum dose 750mg	AUC 3.75 Maximum dose 562.5mg	AUC 2.5 Maximum dose 375mg	Discontinue
Pemetrexed	500mg/m2	375 mg/m2	250 mg/m2	Discontinue
Pembrolizumab/placebo	200 mg fixed dose	Dose reductions are not permitted	Dose reductions are not permitted	Dose reductions are not permitted

5.2.1.2.1 Dose Modification and Toxicity Management Guidelines for Pembrolizumab

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

AEs associated with pembrolizumab exposure may represent an immunologic etiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than on body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical trial data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab and administer corticosteroids. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab are provided in [Table 4].

Table 4 Dose Modification and Toxicity Management Guidelines for Immune-related Adverse Events 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 participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment • Add prophylactic antibiotics for opportunistic infections
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus). • Participants with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
	Grade 4	Permanently discontinue		

AST / ALT elevation or Increased bilirubin	Grade 2	Withhold	• Administer corticosteroids (initial dose of 0.5- 1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable
	Grade 3 or 4	Permanently discontinue	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold	• Initiate insulin replacement therapy for participants with T1DM • Administer anti-hyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes.
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated.	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hypothyroidism	Grade 2-4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyroinine) per standard of care	• Monitor for signs and symptoms of thyroid disorders.
Nephritis and Renal dysfunction	Grade 2	Withhold	• Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper.	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1 or 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		

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: Gullain-Barre Syndrome, encephalitis		
	Grade 4 or recurrent Grade 3	Permanently discontinue		
1. Withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician. **NOTE:** For participants with Grade 3 or 4 immune-related endocrinopathy where withhold of pembrolizumab is required, pembrolizumab may be resumed when AE resolves to ≤ Grade 2 and is controlled with hormonal replacement therapy or achieved metabolic control (in case of T1DM).				

Dose modification and toxicity management of infusion-reactions related to pembrolizumab

Pembrolizumab may cause severe or life threatening infusion-reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab associated infusion reaction are provided in [Table 5].

Table 5 Pembrolizumab Infusion Reaction Dose Modification and Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g. from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of analgesic).

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: Epinephrine** IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Oxygen Pressors Corticosteroids Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. **Subject is permanently discontinued from further study drug treatment.**	No subsequent dosing
Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE) at http://ctep.cancer.gov		

Other allowed dose interruption for pembrolizumab

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

5.2.1.2.2 Dose Modification for Chemotherapy

Recommended dose modifications for key chemotherapy toxicities are outlined in [Table 6] and [Table 7]. These serve as a guide and do not replace investigator judgment and applicable local label recommendations if more stringent.

Table 6 Recommended Dose Modifications for Chemotherapy Hematological Toxicity

		Pemetrexed	Cisplatin/Carboplatin
Platelets	**ANC**	**Dose level (DL) from Table 3**	
≥50,000/mcL AND	≥ 500/mcL	DL 0	DL 0
≥50,000/mcL AND	< 500/mcL	DL -1	DL -1
<50,000/mcL without bleeding AND	ANY	DL -1	DL -1
<50,000/mcL with Grade ≥ 2 bleeding AND	ANY	DL -2	DL -2
ANY AND	< 1,000/mcL + fever ≥ 38.5°C (101°F)	DL -1	DL -1

Table 7 Recommended Dose Modifications for Chemotherapy Non-Hematological Toxicity

		Pemetrexed	Cisplatin	Carboplatin
Event	**CTC Grade**	**Dose level (DL) from Table 3**		
Nausea or vomiting	Grade 3or 4	DL 0	DL 0	DL 0
Diarrhea	Grade 3or 4	DL -1	DL -1	DL 0
Mucositis	Grade 3or 4	DL -2	DL 0	DL 0
Neurotoxicity	Grade 2	DL 0	DL -2	DL 0
	Grade 3or 4	DL -1	Discontinue	DL -1
Transaminase elevation	Grade 3	DL -1	DL -1	DL -1
	Grade 4	Discontinue	Discontinue	Discontinue
Other non-hematological toxicity	Grade 3or 4	DL -1	DL -1	DL -1

Creatinine clearance (CrCl):

CrCl will be based on the original weight-based Cockcroft and Gault formula (Section 12.5). CrCl must be ≥45mL/min prior to the administration of chemotherapy. Pemetrexed and/or platinum may be delayed for up to 42 days to allow the subject time to recover from the toxicity. If a subject's CrCl value has not returned to ≥45 mL/min within 42 days after the previous dose, platinum and/or pemetrexed must be discontinued.

5.2.2 Timing of Dose Administration

Subjects will receive blinded pembrolizumab 200 mg or saline placebo together with pemetrexed 500mg/m^2 (with vitamin supplementation) + cisplatin 75 mg/m^2 OR carboplatin AUC 5 all on Day 1 Q3W for 4 cycles followed by blinded pembrolizumab 200 mg or saline placebo together with pemetrexed 500 mg/m^2 Q3W until progression/completion.

Trial treatment should be administered on Day 1 of each cycle after all procedures / assessments have been completed. Trial treatment can be administered ±3 days of the targeted Day 1 for each cycle, except Cycle 1 when treatment can only be administered +3 days of the targeted Day 1.

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

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

5.2.2.1 Pembrolizumab/Placebo

Pembrolizumab/saline placebo 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 reconstitution, preparation of the infusion fluid, and administration.

5.2.2.2 Pemetrexed

Pemetrexed 500 mg/m^2 will be administered as an IV infusion over 10 minutes Q3W until progression or unacceptable toxicity. All subjects should receive the appropriate supplementation of vitamin B12 and folic acid and corticosteroid prophylaxis as listed below (or as per local label):

- Folic Acid 350-1000 µg oral: at least 5 doses of folic acid must be taken during the 7 days preceding the first dose of pemetrexed, and folic acid dosing must continue during the full course of therapy and for 21 days after the last dose of pemetrexed.
- Vitamin B12 1000 µg IM injection in the week preceding the first dose of pemetrexed and once every 3 cycles thereafter. Subsequent vitamin B12 injections may be given the same day as pemetrexed administration.
- Dexamethasone prophylaxis 4 mg, orally twice per day (or equivalent). Taken the day before, day of, and day after pemetrexed administration. Higher or additional doses are permitted for antiemetic prophylaxis during cycles 1-4 but not to exceed doses in MASCC guidelines (Section 12.6).

5.2.2.3 Cisplatin

Cisplatin 75mg/m^2 should be infused approximately 30 minutes after the pemetrexed infusion for the first 4 cycles and should be immediately preceded and followed by hydration procedures and administered according to local practice and labels.

5.2.2.4 Carboplatin

Carboplatin AUC 5 mg/mL/min will be administered as an IV infusion over 15-60 minutes Q3W for 4 cycles immediately after pemetrexed as per local practice and labels.

5.2.2.5 Antiemetic Therapy

Antiemetic therapy should follow MASCC guidelines (http://www.mascc.org/antiemetic-guidelines) and should, for the first four cycles, include a 5-HT$_3$ receptor antagonist, dexamethasone (or equivalent) and aprepitant (or equivalent) as per the MASCC guidelines.

5.2.3 Trial Blinding/Masking

This is a double-blinded trial; therefore, the subject, the investigator and Sponsor personnel or delegate(s) who are involved in the treatment administration or clinical evaluation of the subjects are unaware of the group assignments. The chemotherapy agents will be open-label. The Sponsor, investigator and subject will not know whether the treatment administered contains pembrolizumab or saline placebo. The study site's unblinded pharmacist will obtain each subject's study identification number and study drug assignment from the interactive voice response system (IVRS)/interactive web response system (IWRS) and prepare the solutions for infusion. The unblinded pharmacist will provide the investigative staff with

ready-to-use blinded pembrolizumab/saline infusion solutions, packaged identically in order to maintain the blinding, for administration at scheduled infusion visits.

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

5.3 Randomization

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 2:1 ratio to pembrolizumab and chemotherapy or saline placebo and chemotherapy, respectively. The choice of cisplatin or carboplatin treatment will be determined prior to randomization and documented in the IVRS/IWRS. The 2:1 ratio of pembrolizumab to chemotherapy is intended to enhance subject accrual.

5.4 Stratification

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

1. PD-L1 expression: Tumor Proportion Score ≥1% vs <1%. PD-L1 inevaluable subjects will be included with the TPS <1% group.
2. Platinum chemotherapy: cisplatin vs carboplatin
3. Smoking status: never vs former/current

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 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 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 (eCRF) 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 eCRF.

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

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

Colony-Stimulating Factors

Routine use of colony-stimulating factors (CSFs) is not permitted. American Society of Clinical Oncology guidelines for use of CSFs should be followed [42].

Nonsteroidal Anti-Inflammatory Drugs

Subjects taking NSAIDs or salicylates will not take the NSAID or salicylate (other than an aspirin dose ≤1.3 grams per day) for 2 days before, the day of, and 2 days after receiving pemetrexed. Subjects taking NSAIDs or salicylates with a long half-life (for example, naproxen, piroxicam, diflunisal, or nabumetone) will not take the NSAIDs or salicylates for 5 days before, the day of, and 2 days after pemetrexed.

5.5.2 Prohibited Concomitant Medications

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

- Antineoplastic systemic chemotherapy or biological therapy not specified in this protocol.
- Immunotherapy not specified in this protocol.
- Chemotherapy not specified in this protocol.
- Investigational agents other than pembrolizumab.
- Radiation therapy; radiotherapy for symptom management is allowed.

  Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed at the Investigator's discretion
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed.
- Prolonged therapy with systemic glucocorticoids (>7 days) for any purpose other than to modulate symptoms from an immune-related Adverse Event (as listed in Section 5.6.1) or for use as a pre-medication for chemotherapeutic agents specified in the protocol. Brief, limited use of systemic corticosteroids (≤7 days) are permitted where such use is considered standard of care (e.g. as pre-medication for contrast allergy or for COPD exacerbation). Replacement doses of steroids (for example, prednisone 10 mg daily) are permitted while on study. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.
- Phenytoin during therapy with cisplatin/carboplatin.

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

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

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

5.6 Rescue Medications & Supportive Care

5.6.1 Supportive Care Guidelines

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of adverse events with potential immunologic etiology are outlined in [Table 4]. Where appropriate, these guidelines include the use of oral or intravenous treatment with corticosteroids as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab.

Note: if after the evaluation the event is determined not to be related, the investigator does not need to follow the treatment guidance. Refer to [Table 4] in Section 5.2.1 for guidelines regarding dose modification and supportive care.

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

5.6.2 Pemetrexed-Related Toxicity

Leucovorin is allowed: (1) for treatment of CTCAE Grade 4 leukopenia or Grade 4 neutropenia lasting more than 3 days, beginning on the third day of Grade 4 myelosuppression; or (2) immediately for treatment of Grade 4 thrombocytopenia, bleeding associated with Grade 3 thrombocytopenia, or Grade 3 or 4 mucositis.

The following doses and schedules are recommended for intravenous use:

- leucovorin 100 mg/m^2 intravenously once, followed by
- leucovorin 50 mg/m^2 intravenously every 6 hours for 8 days.

Appropriate doses of the oral formulation may also be used at the investigator's discretion.

5.7 Diet/Activity/Other Considerations

5.7.1 Diet

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

5.7.2 Contraception

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

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

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

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

OR

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

OR

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

Female and male subjects of reproductive potential must agree to avoid becoming pregnant or impregnating a partner, respectively, while receiving study drug and for 120 days after the last dose of study drug or 180 days after the last dose of chemotherapeutic agents by complying with one of the following:

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

OR

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

Acceptable methods of contraception are[‡]:

Single method (one of the following is acceptable):

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

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

- diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide)
- cervical cap with spermicide (nulliparous women only)
- contraceptive sponge (nulliparous women only)
- male condom or female condom (cannot be used together)

- hormonal contraceptive: oral contraceptive pill (estrogen/progestin pill or progestin-only pill), contraceptive skin patch, vaginal contraceptive ring, or subcutaneous contraceptive injection

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

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

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study, subjects of childbearing potential must adhere to the contraception requirement (described above) from the day of study medication initiation (or 14 days prior to the initiation of study medication for oral contraception) throughout the study period up to 120 days after the last dose of trial therapy or through 180 days after the last dose of chemotherapeutic agents as specified in the protocol. If there is any question that a subject of childbearing potential will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

5.7.3 Use in Pregnancy

If a female subject inadvertently becomes pregnant while on treatment in this study, the subject will immediately be discontinued from trial treatment. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the Sponsor without delay and within 24 hours if the outcome is a serious adverse experience (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.

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 for CR or after receiving the maximum 35 treatments, 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.
- Investigator's decision to withdraw the subject from the trial
- The subject is lost to follow-up
- Administrative reasons

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

- The subject or legal representative (such as parent or legal guardian) requests to discontinue treatment.
- Unacceptable adverse experiences as described in Section 7.2.
- Intercurrent illness that prevents further administration of treatment
- Confirmed radiographic disease progression outlined in Section 7.1.5 (exception if the Sponsor approves treatment continuation)
  Note: If a subject has confirmed progression of disease by RECIST 1.1, the subject may be unblinded and have the opportunity to crossover to receive open-label pembrolizumab monotherapy if he/she was receiving saline placebo and meets all crossover criteria defined in Section 7.1.5.5; a subject who was receiving pembrolizumab and is deemed to be clinically benefiting despite progression will have the opportunity to continue open-label pembrolizumab monotherapy. 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.

  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 (eg, cord compression) requiring urgent alternative medical intervention.
- Any progression or recurrence of any malignancy, or any occurrence of another malignancy that requires active treatment

- Intercurrent illness other than another malignancy as noted above that prevents further administration of treatment
- Recurrent Grade 2 pneumonitis
- A confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements
- Investigator's decision to withdraw the subject from trial treatment
- Completion of 35 treatments (approximately 2 years) with pembrolizumab/placebo

  Note: The number of treatments is calculated starting with the first dose. Subjects who stop the combination or pembrolizumab after receiving 35 doses may be eligible for retreatment if they progress after stopping trial treatment provided they meet the requirements detailed in Section 7.1.5.4. Subjects may be retreated in the Second Course Phase (Retreatment) for up to an additional 17 cycles (approximately 1 year).
- Discontinuation of treatment may be considered for subjects who have attained a confirmed complete response (CR) and have been treated for at least 8 cycles (at least 24 weeks), receiving 2 cycles of the combination including 2 doses of pembrolizumab/placebo beyond the date when the initial CR was declared.

  Subjects who stop the combination with stable disease (SD), partial response (PR), or CR, may be eligible for up to 1 year (17 cycles) of pembrolizumab if they experience disease progression after stopping combination trial treatment. This retreatment is termed the Second Course Phase (Retreatment) and is described in detail in Section 7.1.5.4.

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

- The End of Treatment and Follow-up visit procedures are listed in Section 6 - Trial Flow Chart and Section 7.1.5 - Visit Requirements. After the end of treatment, each subject will be followed for a minimum of 30 days for adverse event monitoring even if the subject started new antineoplastic treatment (serious adverse events will be collected for up to 90 days following cessation of Sponsor's product, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier as described in Section 7.2.3.1). Subjects will have post-treatment follow-up for disease status until disease progression, initiating a non-study cancer treatment, withdrawing consent, becoming lost to follow-up or entering the Second Course Phase. After documented disease progression each subject will either move into the Second Course Phase or be followed for overall survival until death or withdrawal of consent.

  This study will be considered **complete** in terms of primary endpoint following the final analysis of PFS, after the pre-specified number of PFS events.

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 study-related phone-call or visit, discontinues from the trial or is lost to follow-up (i.e. the subject is unable to be contacted by the investigator).

5.11 Clinical Criteria for Early Trial Termination

The clinical trial may be terminated early if the extent (incidence and/or severity) of emerging effects/clinical endpoints is such that the risk/benefit ratio to the trial population as a whole is unacceptable. In addition, further recruitment in the trial or at (a) particular trial site(s) may be stopped due to insufficient compliance with the protocol, 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 Initial Treatment Phase

Details regarding the procedures listed in this table are outlined in Section 7.0.

	Screening Phase	Treatment Cycles (3-Week Cycles)								End of Treatment	Post Treatment		
Treatment Cycle	**Screening (Visit 1)**	**1**	**2**	**3**	**4**	**5**	**6 to 17**	**18 to 35**	**36 +**	**Discon**	**Safety Follow-up**	**Follow-up Visits**	**Survival Follow-up[1]**
Scheduling Window (Days):[2]	**-28 to -1**	**+3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At Time of Discon**	**30 Days Post Discon**	**Every 6 Weeks Post Safety Follow-up ±7 days**	**Every 12 Weeks ±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												
Prior and Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X[19]	X[19]
NSCLC Disease Details and Prior Treatment	X												
Obtain allocation number using IVRS[17]		X											
Subsequent antineoplastic therapy status										X	X	X	X
Survival Status[1]		<--->											X
Clinical Procedures / Assessments													
Review Adverse Events		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		
Vital Signs and Weight	X	X[3]	X	X	X	X	X	X	X	X	X		
SpO2	X	X	X	X	X	X	X	X	X	X	X		
12-Lead ECG	X												
ECOG Performance Status	X[4]	X[18]	X	X	X	X	X	X	X	X	X	X	

	Screening Phase	Treatment Cycles (3-Week Cycles)								End of Treatment	Post Treatment		
Treatment Cycle	**Screening (Visit 1)**	**1**	**2**	**3**	**4**	**5**	**6 to 17**	**18 to 35**	**36 +**	**Discon**	**Safety Follow-up**	**Follow-up Visits**	**Survival Follow-up[1]**
Scheduling Window (Days):[2]	**-28 to -1**	**+3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At Time of Discon**	**30 Days Post Discon**	**Every 6 Weeks Post Safety Follow-up ±7 days**	**Every 12 Weeks ±14 days**
Laboratory Procedures / Assessments: Analysis Performed by Local Laboratory[6]													
Pregnancy Test - Urine or Serum β-HCG [5]	X												
PT/INR and aPTT/PTT	X[4]												
CBC with Differential [6]	X[4]		X	X	X	X	X	X	X	X	X		
Comprehensive Chemistry Panel[6]	X[4]		X	X	X	X	X	X	X	X	X		
Creatinine Clearance Calculation	X[4]		X	X	X	X	X	X	X	X	X		
Urinalysis[6]	X[4]						X[7]	X[7]	X[7]	X	X		
T3 or FT3, FT4 and TSH [6]	X[4]		X		X		X[8]	X[8]	X[8]	X	X		
KL-6, SP-D	X		X	X	X	X	X	X	X	X	X		
Analysis Performed by Central Laboratory													
Pembrolizumab Pharmacokinetics [9]		X	X		X		X	X					
Anti-pembrolizumab Antibodies [9]		X	X		X		X	X					
Blood for Genetics (DNA)[15]		X											
Pharmacokinetics for Pemetrexed, Carboplatin and Cisplatin[14]		X	X		X								
Blood for Correlative Studies (DNA and RNA)		X	X	X						X[16]			
Blood for Biomarker Studies (Plasma and Serum)		X											
Tumor Tissue Collection													
Newly Obtained Tissue Collection for PD-L1 Biomarker Analysis	X												
Efficacy Measurements													
Tumor Imaging	X			X[10]		X[10]	X[10]	X[11]	X[11]	X[12]		X[12]	
Study Drug Administration													
Cisplatin or carboplatin		X	X	X	X								

	Screening Phase	Treatment Cycles (3-Week Cycles)								End of Treatment	Post Treatment		
Treatment Cycle	**Screening (Visit 1)**	**1**	**2**	**3**	**4**	**5**	**6 to 17**	**18 to 35**	**36 +**	**Discon**	**Safety Follow-up**	**Follow-up Visits**	**Survival Follow-up[1]**
Scheduling Window (Days):[2]	**-28 to -1**	**+3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At Time of Discon**	**30 Days Post Discon**	**Every 6 Weeks Post Safety Follow-up ±7 days**	**Every 12 Weeks ±14 days**
Pemetrexed		X	X	X	X	X	X	X	X				
Pembrolizumab or Saline Placebo		X	X	X	X	X	X	X					
Patient Reported Outcomes (PRO)													
EuroQol (EQ)-5D[13]		X	X	X	X	X	X	X	X	X	X		
EORTC QLQ-C30[13]		X	X	X	X	X	X	X	X	X	X		
EORTC QLQ-LC13[13]		X	X	X	X	X	X	X	X	X	X		

1. After documented disease progression, or the start of new anti-cancer treatment; contacts are approximately every 12 weeks by telephone. Updated survival status may be requested by the Sponsor at any time during the course of the study. Upon Sponsor notification, all participants who do not/will not have a scheduled study visit or study contact during the Sponsor-defined time period will be contacted for their survival status (excluding participants who have a death event previously recorded).
2. In general, the window for each visit is ± 3 days unless otherwise noted.
3. Height will be measured only at Visit 1.
4. ECOG and laboratory tests for screening are to be performed within 10 days prior to the first dose of trial treatment.
5. For women of reproductive potential, a urine pregnancy test should be performed within 72 hours prior to first dose of trial treatment. A serum test can be considered if urine is not appropriate. Monthly pregnancy testing should be conducted as per local regulations where applicable.
6. After Cycle 1, lab samples can be collected up to 3 days prior to Day 1 of subsequent cycles.
7. To be repeated every 6 cycles after beginning with Cycle 6.
8. To be repeated every other Cycle beginning with Cycle 6.
9. **Pre-dose trough for both PK and anti-pembrolizumab antibody samples** will be collected at Cycles 1, 2, 4, 6, 8 and every 4 cycles thereafter, and 30 days after discontinuation of study drug (or until the subject starts new anti-cancer therapy). All pre-dose trough samples should be drawn within 24 hours before infusion of pembrolizumab/saline placebo. Additional post-dose peak PK samples will be drawn within 30 minutes after end of pembrolizumab/saline placebo infusion at Cycles 1 and 8. An additional single PK sample should be drawn at 24 hours (Day 2), between 72 and 168 hours (Day 4-8) and 336 hours (Day 15) after Cycle 1 dosing. Collection windows are found in the Procedures Manual.
10. Imaging performed at 6 weeks (± 7 days) and 12 weeks (± 7 days) and then every 9 weeks (63 days ± 7 days) for the first 48 weeks in the treatment period.
11. Imaging performed every 12 weeks (84 days ± 7 days) subsequently.
12. If a previous scan was obtained within 4 weeks prior to the date of discontinuation, then a scan at treatment discontinuation is not mandatory. Follow up scans to be performed using the same imaging schedule used while on treatment (that is, every 6 or 9 weeks in year 1 or 12 weeks after year 1).
13. In year 1 (Cycles 1 to 17), PROs are completed at Cycles 1 through 5 and then every 3rd cycle (every 9 weeks) while on treatment; in years 2 and 3 (Cycle 18 and beyond), PROs are completed every 4th cycle (every 12 weeks) while on treatment. PROs are also completed at treatment discontinuation visit and 30-day safety follow-up visit. See

Section 7 for additional details.
14. Details on collection times are presented in Section 6.1.1.
15. This sample should be drawn for planned analysis of the association between genetic variants in DNA and drug response. If there is either a documented law or regulation prohibiting collection, or if the IRB/IEC does not approve the collection of the sample for these purposes, then this sample will not be collected at that site. If the sample is collected, leftover extracted DNA will be stored for future biomedical research if the subject signs the FBR consent. If the planned genetic analysis is not approved, but FBR is approved and consent is given, this sample will be collected for the purpose of FBR.
16. At treatment discontinuation if subject discontinues prior to Cycle 3.
17. Obtaining allocation number should be performed within 3 days prior to the first dose of trial treatment.
18. Does not have to be done if Screening ECOG was performed within 3 days prior to Cycle 1.
19. After the Safety Follow-up Visit record all medications taken for SAEs and ECIs as defined in Section 7.2.

6.1.1 Pharmacokinetic Collection Schedule for Pemetrexed, Carboplatin and Cisplatin

Sample collection will be in a sub-set of subjects, see Section 7.1.3.2.2 for details.

	Cycle 1 (21 Days)											**Cycle 2 (21 Days)**				**Cycle 4 (21 Days)**			
Cycle Day	1	1	1	1	1	1	1	1	2	3	4	1	1	1	2	1	1	1	2
Time Points (hours)[5]	Pre	Post (end of infusion)	.5	1	2	4	6	8	24	48	72	Pre	Post	2	24	Pre	Post	2	24
Pemetrexed	X[1]	X[2]	X	X	X	X		X	X[3]	X[3]	X[3]								
Carboplatin	X[1]	X[2]		X[4]	X	X	X	X	X[3]										
Cisplatin	X[1]	X[2]			X				X[3]			X[1]	X[2]	X	X[3]	X[1]	X[2]	X	X[3]

Please note: Actual drug dosing and PK/pharmacodynamic sampling times have to be documented by the sites and will be captured in the database.

Sample collection must be from opposite arm to that used for study drug administration/infusion. If drug was administered via a central venous catheter, sample collection for PK should be from a different site.

1. Predose collection should be within 60 minutes of dosing (hour 0) each cycle PK is collected.
2. Post-dose collection should be within 15 minutes after the end of infusion. The infusion duration for pemetrexed is 10 minutes (0.17 hour), carboplatin is 15-60 minutes, and cisplatin is 30 minutes. The detail of PK collection including time window is written in the Procedure Manual.
3. Window: ±2 hours.
4. Carboplatin is planned to be administered as an IV infusion over 15 to 60 minutes Q3W for 4 cycles immediately after pemetrexed. If infusion duration is 45-60 min, then 1 hour sample can be eliminated as end of infusion sample collection (Post) would cover this 1 hour time point.
5. Time relative to initiation of each drug administration.

6.2 Second Course Phase (Retreatment)

Details regarding the procedures listed in this table are outlined in Section 7.0. Second course retreatment subjects may receive up to 17 cycles (approximately 1 year) of pembrolizumab therapy.

Trial Period:	**Treatment Cycles (3-Week Cycles)**						**End of Treatment**	**Post-Treatment**		
Treatment Cycle/Title:					**To be Repeated Beyond 6 Cycles**		**Discon**	**Safety Follow-up**	**Follow Up Visits**	**Survival Follow-up[1]**
	1	**2**	**3**	**4**	**5**	**6**				
Scheduling Window (Days)[2]:	**+3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At Time of Discon**	**30 Days Post Discon**	**Every 6 Weeks Post Safety Follow up ±7 days**	**Every 12 Weeks ±14 days**
Administrative Procedures										
Eligibility Criteria	X									
Concomitant Medication Review	X	X	X	X	X	X	X	X	X[9]	X[9]
Subsequent antineoplastic therapy status							X	X	X	X
Survival Status[1]	<-->									X
Clinical Procedures/Assessments										
Review Adverse Events	X	X	X	X	X	X	X	X	X	
Full Physical Examination	X									
Directed Physical Examination		X	X	X	X	X	X	X		
Vital Signs	X	X	X	X	X	X	X	X		
SpO2	X	X	X	X	X	X	X	X		
ECOG Performance Status	X	X	X	X	X	X	X			
Laboratory Procedures/Assessments: analysis performed by LOCAL laboratory										
Pregnancy Test – Serum or Urine[3]	X									
Hematology[4]	X[5]	X	X	X	X	X	X	X		
Chemistry Panel[4]	X[5]	X	X	X	X	X	X	X		
Urinalysis[4]	X[5]				X[6]		X	X		
T3 or FT3, FT4, TSH[4]	X[5]		X		X[6]		X	X		
KL-6, SP-D	X	X	X	X	X	X	X	X		
Efficacy Measurements										
Tumor Imaging	X[7]				X[8]	X[8]	X[8]		X[8]	
Study Drug Administration										
Pembrolizumab	X	X	X	X	X	X				

1. After documented disease progression, or the start of new anti-cancer treatment; contacts are approximately every 12 weeks by telephone. Updated survival status may be requested by the Sponsor at any time during the course of the study. Upon Sponsor notification, all participants who do not/will not have a scheduled study visit or study contact during the Sponsor-defined time period will be contacted for their survival status (excluding participants who have a death event previously recorded).
2. In general, the window for each visit is ± 3 days unless otherwise noted.
3. For women of reproductive potential, a urine pregnancy test should be performed within 72 hours prior to first dose of trial treatment. A serum test can be considered if urine is not appropriate. Monthly pregnancy testing should be conducted as per local regulations where applicable.
4. After Cycle 1, lab samples can be collected up to 3 days prior to the scheduled time point.
5. Laboratory tests for determining eligibility for retreatment are to be performed within 10 days prior to the first retreatment dose of pembrolizumab.
6. To be repeated every 4 cycles after Cycle 5.
7. A scan must be performed within 30 days prior to restarting treatment with pembrolizumab.
8. Imaging performed every 12 weeks (84 ± 7 days).
9. After the Safety Follow-up Visit record all medications taken for SAEs and ECIs as defined in Section 7.2.

6.3 Crossover Phase

Only applicable for subjects who are unblinded after verification of PD by BICR and deemed eligible for the crossover phase if initially in the placebo arm or for continued treatment despite PD in the pembrolizumab arm. Subjects may receive up to a total of 35 cycles (approximately 2 years) of pembrolizumab monotherapy. Details regarding the procedures listed in this table are outlined in Section 7.0.

	Treatment Cycles[1]														End of Treatment Phase		Follow up Phase[8]			Survival Follow up[11]
Treatment Cycle / Scheduled Time	**1[4]**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14 through 35**	**Discontinuation Visit[6]**	**Safety Follow up Visit [7]**	**Follow up Visit 1**	**Follow up Visit 2**	**Follow up Visit 3 and Beyond**	**Survival Follow up Visit 1 and Beyond**
Scheduling Window (Days):	**+3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At Study Drug Discontinuation ±3**	**30 Days From Last Dose ± 3**	**3 Months From Last Dose ± 7**	**6 Months From Last Dose ± 7**	**Every 3 Months After Visit 2 ±7**	**Every 3 Months ±14**
Administrative Procedures																				
Prior and Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[12]			X[12]
Subsequent antineoplastic therapy status															X	X	X	X	X	X
Survival Status[11]	<--->																			X
Clinical Procedures / Assessments																				
Review Adverse Events [9]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Full Physical Examination	X																			
Directed Physical Examination		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Vital Signs and Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
SpO2	X	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	X		
Laboratory Procedures / Assessments: analysis performed by local laboratory[2]																				
CBC with Differential	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
PT/INR and aPTT/PTT	X																			
Comprehensive	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				

	Treatment Cycles[1]														End of Treatment Phase		Follow up Phase[8]			Survival Follow up[11]
Treatment Cycle / Scheduled Time	**1[4]**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14 through 35**	**Discontinuation Visit[6]**	**Safety Follow up Visit [7]**	**Follow up Visit 1**	**Follow up Visit 2**	**Follow up Visit 3 and Beyond**	**Survival Follow up Visit 1 and Beyond**
Scheduling Window (Days):	**+3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At Study Drug Discontinuation ±3**	**30 Days From Last Dose ± 3**	**3 Months From Last Dose ± 7**	**6 Months From Last Dose ± 7**	**Every 3 Months After Visit 2 ±7**	**Every 3 Months ±14**
Chemistry Panel																				
Urinalysis	X				X				X				X	X	X	X				
T3 or FT3, FT4 and TSH	X	X		X		X		X		X		X		X	X	X				
KL-6, SP-D	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Efficacy Measurements																				
Tumor Imaging[3]	X				X				X				X	X	X[10]		X[10]	X[10]	X[10]	
Study Drug Administration																				
Pembrolizumab[5]	X	X	X	X	X	X	X	X	X	X	X	X	X	X						

1. In general, assessments/procedures are to be performed on Day 1 and prior to the first dose of trial treatment for each cycle unless otherwise specified. Treatment cycles are 3 weeks (21 days ± 3 days). If treatment cycles are adjusted all procedures except imaging will be completed according to the Cycle number and not weeks on treatment, imaging will be performed every 12 weeks (84 days ± 7 days) from the first dose of trial treatment regardless of any treatment delays.
2. Laboratory tests for screening are to be performed within 10 days prior to the first dose of trial treatment. After Cycle 1, lab samples can be collected up to 72 hours prior to the scheduled time point. Laboratory results must be known prior to dosing. Urinalysis: perform every 6 cycles after Cycle 13. T3 or FT3, FT4, and TSH: perform every 2 cycles after Cycle 14; thyroid function tests will be performed by a central lab only if the local laboratory is unable to perform this service. See Section 7.1.3 for details regarding laboratory tests.
3. Blinded central review verifying progressive disease is: 1) required for crossover, without exception, and 2) is based on RECIST 1.1. Tumor response assessment is required every 12 weeks (84 days±7 days) until the subject starts another anti-cancer treatment. Assessment of disease response or progression will be determined by the investigator. The treating physician will record a physician assessed tumor response and the criteria used, i.e., immune-related RECIST or standard RECIST v 1.1 on the discontinuation form.
4. Screening can initiate once progressive disease have been verified by the blinded central radiology review. All procedures and assessments completed at the time of withdrawal from the main study may be used as appropriate for the start of the Crossover Phase of the study.
5. Treatment with Pembrolizumab should not initiate until at least 21 days after the last dose of chemotherapy regardless of the time of progression. Pembrolizumab can be administered for up to 2 years.
6. 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.
7. 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 three Safety Follow-up Visits, one after the Treatment Phase, Crossover Phase and 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.

8. Subjects who stop pembrolizumab after 35 trial treatments and have achieved PR and/or SD OR have achieved a CR (see Section 7.1.5.5) 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. 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. Once a subject discontinues study treatment, report all SAEs (related and unrelated to trial treatment) occurring within 90 days following cessation of treatment or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, and ECIs occurring within 30 days following cessation of treatment. After this time, report only SAEs that are considered related to trial treatment.
10. Tumor imaging is not needed for subjects who start another anti-cancer treatment regimen.
11. Once the subject stops the imaging assessments for this protocol (eg, 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 12 weeks 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 participants who do not/will not have a scheduled study visit or study contact during the Sponsor-defined time period will be contacted for their survival status (excluding participants who have a death event previously recorded).
12. After the Safety Follow-up Visit record all medications taken for SAEs and ECIs as defined in Section 7.2.

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.

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

7.1.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee. Medical history will include all active conditions, and any condition diagnosed within the prior 10 years that are considered to be clinical significant by the Investigator. Details regarding the subject's lung cancer will be recorded separately and not listed as medical history.

The investigator or qualified designee will obtain prior and current details regarding the subject's lung cancer.

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 during the screening period (Day -30 through Day -1 of trial treatment start). Prior anti-cancer treatment for NSCLC will be recorded separately and not listed as a prior medication.

The investigator or qualified designee will review and record all prior anti-cancer treatments including systemic treatments, radiation, and surgeries, regardless of the time prior to first dose of trial treatment.

7.1.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the subject during the trial through the Safety Follow-up Visit. In addition, new medications started during the Crossover Phase and Second Course Phase through the Crossover Safety Follow-up Visit and Second Course Phase Safety Follow-up Visit, respectively, should be recorded.

All medications related to reportable SAEs and ECIs should be recorded as defined in Section 7.2.

7.1.1.5.3 Subsequent Anti-Cancer Therapy Status

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

7.1.1.6 Assignment of Screening Number

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

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

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

7.1.1.7 Assignment of Treatment/Randomization Number

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

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

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

Interruptions from the protocol specified treatment plan for greater than 12 weeks between pembrolizumab doses for non-drug-related or administrative reasons (see Section 5.2.1.2 for drug-related modifications) require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on subject management.

Trial medication will be administered by site and/or institution staff per local SOPs and guidelines. The total volume of pembrolizumab infused will be compared to the total volume prepared to determine compliance to each dose of pembrolizumab administered.

The instructions for preparing and administering pembrolizumab will be provided in the Pharmacy Manual.

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 12.7). Toxicities

will be characterized in terms including seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

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

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

7.1.2.2 Physical Exam

7.1.2.2.1 Full Physical Exam

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

7.1.2.2.2 Directed Physical Exam

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

7.1.2.3 Vital Signs

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

7.1.2.4 12-Lead Electrocardiogram (ECG)

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

7.1.2.5 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The Investigator or qualified designee will assess ECOG status (see Section 12.8) 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 at Cycle 1 of Initial Treatment Phase does not have to be done if screening ECOG was performed within the prior 3 days.

7.1.2.6 Pulse Oximetry (SpO2)

Pulse oximetry will be performed using local standard procedures once at screening, prior to the administration of each dose of trial treatment, at Discontinuation Visit, and at Safety Follow-up Visit as specified in the Trial Flow Chart.

7.1.2.7 Tumor Imaging and Assessment of Disease

The process for image collection and transmission to the central imaging vendor can be found in the Site Imaging Manual (SIM). Tumor imaging should be acquired by computed tomography (CT, strongly preferred). Magnetic resonance imaging (MRI) should be used when CT is contraindicated or for imaging in the brain. The same imaging technique regarding modality and use of contrast should be used in a subject throughout the trial to optimize the visualization of existing and new tumor burden.

Local site investigator/radiology assessment based on RECIST 1.1 will be used to determine subject eligibility. Although RECIST 1.1 references to maximum of 5 target lesions in total and 2 per organ, Merck allows maximum of 10 target lesions in total and 5 per organ. All scheduled images for all study subjects from the sites will be submitted to the central imaging vendor. In addition, additional imaging (including other modalities) that are obtained at unscheduled time points to determine disease progression, as well as imaging obtained for other reasons but captures radiologic progression, should be submitted to the central imaging vendor.

The central imaging vendor will verify progressive disease (PD) upon request following local site investigator-assessed radiologic evidence of PD. Verification of progression is one of the qualification criteria for Crossover Phase. Expedited verification of radiologic PD by the central imaging vendor will be communicated to the study site and sponsor (See Section 7.1.2.7.5).

7.1.2.7.1 Initial Tumor Imaging

Initial tumor imaging at screening must be performed within 28 days prior to the date of randomization. The site study team must review screening images to confirm the subject has measurable disease per RECIST 1.1. The screening images must be submitted to the central imaging vendor for retrospective confirmation of eligibility.

Scans performed as part of routine clinical management are acceptable for use as screening tumor imaging if they are of diagnostic quality and performed within 28 days prior to the date of randomization and can be assessed by the central imaging vendor.

Subjects with previously treated brain metastases may participate provided they have stable brain metastases. Any neurologic symptoms must have returned to baseline and subjects must have no clinical evidence of new or enlarging brain metastases, and have not used steroids for brain metastases for at least 3 days prior to trial initiation as per local site assessment. This exception does not include carcinomatous meningitis, as subjects with carcinomatous meningitis are excluded regardless of clinical stability.

7.1.2.7.2 Tumor Imaging During the Trial

The first on-study imaging assessment should be performed at 6 weeks (42 days ±7 days) and again at 12 weeks (84 days ±7 days) from the date of randomization. Subsequent tumor imaging should be performed every 9 weeks (63 days ±7 days) or more frequently if clinically indicated. After 48 weeks, subjects who remain on treatment will have imaging performed every 12 weeks (84 days ±7 days). Imaging timing should follow calendar days and should not be adjusted for delays in cycle starts. Imaging should continue to be performed until disease progression verified by central imaging vendor (unless site PI elects to continue treatment and follow irRECIST), the start of new anti-cancer treatment, withdrawal of consent, or death, whichever occurs first. All supplemental imaging must be submitted to the central imaging vendor.

Per RECIST 1.1, partial and complete response should be confirmed by a repeat tumor imaging assessment not less than 4 weeks from the date the response was first documented. The tumor imaging for confirmation of response may be performed at the earliest 4 weeks after the first indication of response, or at the next scheduled scan (i.e. 6, 9 or 12 weeks later), whichever is clinically indicated. Subjects will then return to regular scheduled imaging, starting with the next scheduled imaging time point. Subjects who obtain a confirmation scan do not need to undergo the next scheduled tumor imaging if it is < 4 weeks later; tumor imaging may resume at the subsequent scheduled imaging time point.

Per irRECIST (Section 7.1.2.7.6), disease progression should be confirmed by the site at least 4 weeks after central verification of site-assessed 1st radiologic evidence of PD in clinically stable subjects. Subjects who have unconfirmed disease progression may continue on treatment at the discretion of the site investigator until progression is confirmed by the site provided they have met the conditions detailed in Section 7.1.2.7.6. Subjects who obtain a confirmation scan do not need to undergo the next scheduled tumor imaging if it is < 4 weeks later; tumor imaging may resume at the subsequent scheduled imaging time point if clinically stable. Subjects who have confirmed disease progression as assessed by the site will discontinue the treatment. Exception is detailed in Section 7.1.2.7.6.

7.1.2.7.3 End of Treatment and Follow-up of Tumor Imaging

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

In subjects who discontinue trial treatment without documented disease progression, tumor imaging using the same imaging schedule used while on treatment (every 6 or 9 weeks in year 1 or 12 weeks after year 1) to monitor disease status until (1) the start of new anti-cancer treatment, (2) disease progression, (3) death, or (4) the end of the study, whichever occurs first, should be used.

7.1.2.7.4 Second Course (Retreatment) and Crossover Tumor Imaging

A scan must be performed within 30 days prior to starting/restarting treatment with pembrolizumab. Local reading (investigator assessment with site radiology reading) will be

used to determine eligibility. Imaging should be submitted to the central imaging vendor for retrospective verification.

The first on-study imaging assessment should be performed at 12 weeks (84 days ±7 days) after the start/restart of treatment. Subsequent tumor imaging should be performed every 12 weeks (84 days ±7 days) or more frequently if clinically indicated.

Per RECIST 1.1, partial or complete response should be confirmed by a repeat tumor imaging assessment not less than 4 weeks from the date the response was first documented. The tumor imaging for confirmation of response may be performed at the earliest 4 weeks after the first indication of response, or at the next scheduled scan, whichever is clinically indicated. Subjects will then return to regular scheduled imaging every 12 weeks (84 days ±7 days), starting with the next scheduled imaging time point. Subjects who obtain a confirmation scan do not need to undergo scheduled tumor imaging if it is < 4 weeks later and may wait until the next scheduled imaging time point.

Per irRECIST (Section 7.1.2.7.6), if tumor imaging shows initial PD, tumor assessment should be repeated ≥ 4 weeks later in order to confirm PD with the option of continuing treatment while awaiting radiologic confirmation of progression. Subjects who obtain a confirmation scan do not need to undergo scheduled tumor imaging if it is < 4 weeks later and may wait until the next scheduled imaging time point if clinically stable.

Imaging should continue to be performed until disease progression, the start of new anti-cancer treatment, withdrawal of consent, death, or notification by the Sponsor, whichever occurs first. Disease progression may be confirmed at least 4 weeks after the first tumor imaging indicating progressive disease in clinically stable subjects.

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

In subjects who discontinue trial treatment without documented disease progression, every effort should be made to continue monitoring their disease status by radiologic imaging every 12 weeks (84 days ± 7 days) until (1) the start of new anti-cancer treatment, (2) disease progression, (3) death, or (4) the end of the study, whichever occurs first.

7.1.2.7.5 RECIST 1.1 Assessment of Disease

RECIST 1.1 will be applied by the central imaging vendor as the primary measure for assessment of tumor response, date of disease progression, and as a basis for all protocol guidelines related to disease status (e.g., discontinuation of study therapy). Initial tumor imaging showing site-assessed PD should be submitted to the central imaging vendor immediately only if the investigator intends to cross over without hesitation to pembrolizumab monotherapy. The site will be notified if the central imaging vendor verifies progressive disease (PD) using RECIST 1.1.

7.1.2.7.6 irRECIST Assessment of Disease

irRECIST is RECIST 1.1 adapted as described below to account for the unique tumor response seen with immunotherapeutic drugs. irRECIST will be used by site investigator/local radiology review to assess tumor response and progression, and make treatment decisions. This data will be collected in the clinical database. Treatment efficacy based on irRECIST as assessed by central imaging vendor review will be evaluated retrospectively.

When feasible, subjects should not be discontinued until progression is confirmed by the local site investigator/radiology assessment. This allowance to continue treatment despite initial radiologic progressive disease (PD) takes into account the observation that some subjects can have a transient tumor flare in the first few months after the start of immunotherapy, and then experience subsequent disease response. Subjects that are deemed clinically unstable are not required to have repeat tumor imaging for confirmation of PD. Tumor flare includes any of the following scenarios:

- Worsening of existing target lesion(s)
- Worsening of existing non-target lesion(s)
- Development of new lesions(s)

In subjects who have initial evidence of radiological PD by RECIST 1.1, it is at the discretion of the PI whether to continue a subject on study treatment until repeat imaging is obtained (using irRECIST for subject management, see [Table 8]). This clinical judgment decision by the site should be based on the subject's overall clinical condition, including performance status, clinical symptoms, and laboratory data. Subjects may receive study treatment and tumor assessment should be repeated $\geq$ 4 weeks later in order to confirm PD by irRECIST per site assessment. If PD is confirmed by irRECIST, a request should be submitted to the central imaging vendor to verify PD. Clinical stability is defined as the following:

1) Absence of symptoms and signs indicating clinically significant progression of disease, including worsening of laboratory values

2) No decline in ECOG performance status

3) Absence of rapid progression of disease

4) Absence of progressive tumor at critical anatomical sites (e.g., cord compression) requiring urgent alternative medical intervention

Any subject deemed **clinically unstable** should be discontinued from trial treatment at central verification of site-assessed first radiologic evidence of PD and is not required to have repeat imaging for PD confirmation.

In determining whether or not the tumor burden has increased or decreased per irRECIST, the local site investigator should consider all target and non-target lesions as well as any incremental new lesion(s).

Scenarios where PD is not confirmed at repeat imaging if ALL of the following occur by irRECIST:

- Target lesion sum of diameters is <20% or <5 mm absolute increase compared to nadir
- Non-target disease resulting in initial PD is stable or qualitatively improved
- New lesion resulting in initial PD is stable or qualitatively improved
- No new incremental new lesion(s) since last evaluation
- No incremental new non-target lesion progression since last evaluation

If repeat imaging does not confirm PD per irRECIST as assessed by the local site investigator and the subject continues to be clinically stable, treatment may continue and follow the regular imaging schedule.

Disease progression will be considered to be "confirmed" at repeat imaging if ANY of the following occur (as assessed by irRECIST):

- Target lesion sum of diameters remains ≥20 % and at least 5 mm absolute increase compared to nadir
- Non-target disease resulting in initial PD is qualitatively worse
- New lesion resulting in initial PD is qualitatively worse
- Additional new lesion(s) since last evaluation
- Additional new non-target lesion progression since last evaluation

If repeat imaging confirms PD due to any of the scenarios listed above, subject will be discontinued from study therapy.

NOTE: If a subject has confirmed radiographic progression (i.e. 2 scans at least 4 weeks apart demonstrating progressive disease) per irRECIST, but the subject is achieving a clinically meaningful benefit, and there is no further increase in the tumor burden at the confirmatory tumor imaging, an exception to continue treatment may be considered following consultation with the Sponsor. In this case, if treatment is continued, tumor imaging should continue to be performed following the intervals as outlined in Section 6.0 Study Flowchart and be submitted to the central imaging vendor.

Additional details about irRECIST are referenced in Merck TIP Sheet for RECIST 1 1 and irRECIST.

Table 8 Imaging and Treatment after Radiologic Evidence of PD

	Clinically Stable		Clinically Unstable	
	Imaging	**Treatment**	**Imaging**	**Treatment**
1st radiologic evidence of PD by RECIST 1.1 which has been verified by the central imaging vendor	No additional imaging required	Discontinue treatment (for placebo - transition to Crossover Phase if qualification criteria met; for pembrolizumab – exception is possible upon consultation with sponsor)	Repeat imaging at ≥ 4 weeks to confirm PD per physician discretion only	Discontinue treatment
Repeat tumor imaging confirms PD by irRECIST at the local site and PD verified by central imaging vendor	No additional imaging required	Discontinue treatment (for placebo – transition to Crossover Phase if qualification criteria met; for pembrolizumab - exception is possible upon consultation with sponsor)	At physician discretion	N/A
Repeat tumor imaging shows SD, PR or CR by irRECIST by the local site	Continue regularly scheduled imaging assessments	Continue study treatment at the local site Investigator's discretion	Continue regularly scheduled imaging assessments	May restart study treatment if condition has improved and/or clinically stable per Investigator's discretion. Next tumor image should occur according to the regular imaging schedule outlined in the protocol

CR=complete response; irRECIST=immune-related response evaluation criteria in solid tumors; PD=progressive disease; PFS=progression-free survival; PR=partial response; SD=stable disease

7.1.2.8 Tumor Tissue Collection: PD-L1 Status

All subjects should submit either a newly obtained core or excisional biopsy or archival tissue (FNA is not adequate for both archival and new tissue samples) to a central lab for characterization of PD-L1 status prior to treatment allocation.

> Note: Submission of formalin-fixed paraffin embedded tumor tissue sample blocks are preferred; if submitting unstained slides, the slides should be freshly cut and submitted to the testing laboratory within 14 days from the site slide section date, otherwise a new specimen will be requested.

If the sample is determined to be non-evaluable prior to testing by the central laboratory, a new sample should be submitted if available. This may include additional cut slides that are outside of the 14 day window noted above.

Individual subject PD-L1 status will not be disclosed to investigative sites, study subjects or Sponsor personnel. Analyses by PD-L1 biomarker status will be limited and documented.

If the subject signs the Future Biomedical Research consent, any leftover samples that would be ordinarily discarded at the end of the main study will be retained for Future Biomedical Research.

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 9].

Table 9 Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Blood	Serum β-human chorionic gonadotropin (β-hCG)[a]
Hemoglobin	Alkaline phosphatase	Glucose	PT (INR)[d]
Platelet count	Alanine aminotransferase (ALT)	Protein	aPTT/PTT [d]
White Blood Cell - WBC (total and differential)	Aspartate aminotransferase (AST)	Specific gravity	Total triiodothyronine (T3)[e]
Red Blood Cell Count	Carbon dioxide (CO_2 or Bicarbonate) [b]	Microscopic exam, if abnormal results are noted	Free thyroxine (FT4)
Absolute Neutrophil Count	Calcium	Urine pregnancy test[a]	Thyroid stimulating hormone (TSH)
Absolute Lymphocyte Count	Chloride		Follicle Stimulating Hormone (FSH)[f]
	Creatinine		Blood for correlative studies
	Glucose		Blood for genetics
	Lactate Dehydrogenase		Sialylated carbohydrate antigen KL-6 (KL-6)[g]
	Phosphorus		Surfactant Protein D (SP-D)[g]
	Potassium		
	Sodium		
	Total Bilirubin		
	Direct Bilirubin, if total bilirubin is elevated above the upper limit of normal		
	Total protein		
	Blood Urea Nitrogen		
	Uric acid		
	Urea[c]		

a. Perform on women of childbearing potential only. Urine pregnancy test is preferred. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
b. If these tests are not done as part of standard of care in your region then these tests do not need to be performed.
c. Blood Urea Nitrogen is preferred; if not available urea may be tested.
d. Coagulation factors (PT/INR and aPTT/PTT) should be tested as part of the screening procedures for all subjects. Any subject receiving anticoagulant therapy should have coagulation factors monitored closely throughout the trial.
e. Total T3 is preferred; if not available free T3 may be tested.
f. As needed, FSH to be performed at Screening to confirm post-menopausal status.
g. Serological biomarkers for interstitial lung disease; to be performed at every cycle; required in Japan only

Laboratory tests for screening 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 3 days prior to Day 1 of subsequent cycles.

Results must be reviewed by the investigator or qualified designee and found to be acceptable prior to each dose of trial treatment. Unresolved abnormal labs that are drug related AEs should be followed until resolution. Labs do not need to be repeated after the end of treatment if labs are within normal range.

7.1.3.2 Pharmacokinetic/Pharmacodynamic Evaluations

The following analyses may only be performed if required.

Pembrolizumab

To further evaluate pembrolizumab immunogenicity and pembrolizumab exposure in this indication, and also to evaluate exposure of the proposed dosing regimen, sample collections for analysis of anti-drug antibodies (ADA) and PK are currently planned as shown in the Trial Flowchart (Sections 6.1). Blood samples will be obtained to measure pharmacokinetics of serum pembrolizumab in combination with pemetrexed and carboplatin (or cisplatin). The pembrolizumab serum maximum concentration (C_{max}) and minimum concentration (C_{trough}) at planned visits and times will be summarized. If ongoing ADA and/or PK results continue to be consistent with existing ADA and/or PK data from other pembrolizumab clinical trials, it may be decided to discontinue or reduce further sample collection in this study. Pharmacokinetic data may be analyzed using nonlinear mixed effects modeling. Based on pharmacokinetic (PK) data obtained in this study as well as PK data obtained from other studies, a population PK analysis may performed to characterize pharmacokinetic parameters (Clearance (CL), Volume of distribution (V)) and evaluate the effect of extrinsic and intrinsic factors to support proposed dosing regimen. Pharmacokinetic data will also be used to explore the exposure-response relationships for pembrolizumab antitumor activity/efficacy as well as safety in the proposed patient population, if feasible. The results of these analyses, if performed, will be reported separately.

Exploratory drug-drug interaction analysis

To estimate the effect of pembrolizumab on the pharmacokinetics of pemetrexed and carboplatin (or cisplatin) and, conversely, to estimate the effects of pemetrexed and carboplatin (or cisplatin) on the pharmacokinetics of pembrolizumab, pharmacokinetic studies will be conducted in a subset of research participants enrolled on this protocol.

Since this protocol does not have a pembrolizumab monotherapy arm, the data from other studies can be pooled together to assess the effect of pemetrexed and carboplatin (or cisplatin) on the pharmacokinetics of pembrolizumab. In addition, the pharmacokinetics of pemetrexed and carboplatin (or cisplatin) may be extracted from other studies to confirm results if sample size is too small given variability and imbalanced sample size due to the randomized trial.

The pharmacokinetic parameters, namely the maximum plasma drug concentration (C_{max}), the time to reach C_{max} (T_{max}), the area under the plasma concentration-time curve (AUC) of pemetrexed, carboplatin or cisplatin would be estimated for each patient by standard noncompartmental methods, if feasible. Population pharmacokinetic approach may be used if needed. The observed pharmacokinetics data at planned visits and times will be summarized.

7.1.3.2.1 Blood Collection for Serum Pembrolizumab

Pre-dose trough PK and anti-pembrolizumab antibody samples will be collected at Cycles 1, 2, 4, 6, 8 and every 4 cycles thereafter, 30 days after discontinuation of study drug (or until the subject starts new anti-cancer therapy). All pre-dose trough samples should be drawn within 24 hours before infusion of pembrolizumab/saline placebo.

Additional post-dose peak PK samples will be drawn within 30 minutes after end of pembrolizumab/saline placebo infusion at Cycles 1 and 8. An additional single PK sample should be drawn at 24 hours (Day 2), between 72 and 168 hours (Day 4-8) and 336 hours (Day 15) after Cycle 1 dosing.

Sample collection, storage and shipment instructions for serum samples will be provided in the Procedure Manual. PK samples should be drawn according to the PK collection schedule for subjects who receive pembrolizumab. Every effort should be taken to collect samples at 30 days after end of pembrolizumab treatment.

7.1.3.2.2 Blood Collection for Pemetrexed, Carboplatin or Cisplatin

Pemetrexed

Blood samples for pemetrexed measurement will be collected during Cycle 1 before dosing, at 0.17 h (within 15 minutes after the end of infusion), and at 0.5, 1, 2, 4, 8, 24, 48, and 72 h after the start of the drug infusion. The exact time of sample collection and time of pemetrexed administration will be recorded. Sample collection, storage and shipment instructions for plasma samples will be provided in the Procedure Manual.

Carboplatin

Blood samples for carboplatin measurement will be collected at Cycle 1 before dosing, at the end of the carboplatin infusion, and at 1, 2, 4, 6, 8, 12 and 24 h after the start of the carboplatin administration. The exact time of sample collection and time of carboplatin administration will be recorded. Sample collection, storage and shipment instructions for plasma samples will be provided in the Procedure Manual.

Cisplatin

Pharmacokinetic studies of unbound and total cisplatin will be performed in consenting subjects enrolled on this protocol with the first infusion on Cycle 1, 2, and 4 (three total occasions, if possible). Blood samples will be drawn for pharmacokinetic analyses at the following time points: Pre-dose, immediately at end of infusion (EOI), 2 hours, and 24 hours (±2) after the start of the cisplatin administration. The exact time of sample collection and time of cisplatin administration will be recorded. Sample collection, storage and shipment instructions for plasma samples will be provided in the Procedure Manual.

7.1.3.2.3 Blood Collection for Anti- pembrolizumab Antibodies

Sample collection, storage and shipment instructions for serum samples will be provided in the Procedure Manual. Anti- pembrolizumab antibody samples should be drawn according to the ADA collection schedule (Section 6.1). Every effort should be taken to collect samples at 30 days after end of pembrolizumab/saline placebo treatment for ADA. Simultaneous PK sampling is required for interpretation of ADA analysis.

7.1.3.3 Patient Reported Outcomes (PROs)

The EuroQol (EQ)-5D, EORTC QLQ-C30 and EORTC QLQ-LC13 questionnaires will be administered by trained study site personnel and completed electronically by the subjects themselves.

It is strongly recommended that ePROs are administered prior to drug administration, adverse event evaluation and disease status notification. The ePROs are completed in the following order: EuroQol e(EQ)-5D first, then EORTC eQLQ-C30, and lastly the EORTC eQLQ-LC13 at the time points specified in the Trial Flow Charts and briefly summarized below. The Patient Reported Outcomes (PROs) are assessed as follows (does not include HEA):

- At Cycles 1, 2, 3, 4 and 5
- After the fifth cycle and until the end of year 1 (Cycle 17) they will be assessed every third cycle (every 9 weeks)
- During years 2 and 3 they will be assessed every fourth cycle (every 12 weeks) until PD, while the subject is receiving study treatment.
- At the Treatment Discontinuation Visit.*
- At 30-day Safety Follow-up Visit.*

*If the Treatment Discontinuation Visit occurs 30 days from the last dose of study treatment, at the time of the mandatory Safety Follow up Visit, PROs do not need to be repeated.

7.1.3.4 Blood for Correlative and Biomarker Studies

Blood for correlative studies (RNA and DNA) should be collected pre-dose for each of the following: Day 1, Cycle 1; Day 1 Cycle 2; Day 1 Cycle 3 and at treatment discontinuation if subject discontinues prior to Cycle 3. Blood for biomarker studies (Plasma and Serum) should be collected pre-dose only at Cycle 1 Day 1. Detailed instructions with specific time points per sample are provided in the Procedures Manual. Any leftover samples from the correlative blood studies and biomarker studies will be stored for future biomedical research if the subject signs the FBR consent.

7.1.3.5 Planned Genetic Analysis Sample Collection

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

7.1.3.6 Future Biomedical Research Sample Collection

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

- Leftover DNA for future research
- Leftover DNA and RNA from correlative studies

- Leftover plasma and serum from biomarker studies
- Leftover main study tumor

7.1.4 Other Procedures

7.1.4.1 Withdrawal/Discontinuation

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

When a subject discontinues/withdraws from participation in the trial, all applicable activities scheduled for the end of treatment 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. Subjects who a) attain a CR or b) complete 35 administrations of pembrolizumab (approximately 2 years) may discontinue treatment with the option of restarting treatment if they meet the criteria specified in Section 7.1.5.4. After discontinuing treatment following assessment of CR or 35 administrations of pembrolizumab, these subjects should return to the site for a Safety Follow-up Visit (described in Section 7.1.5.3) and then proceed with assessments (described in Section 7.1.5.3).

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

When the investigator or sub-investigator needs to identify the blinded therapy used by a subject and the dosage administered in case of emergency e.g., the occurrence of serious adverse experiences, he/she will contact the emergency unblinding call center by telephone and make a request for emergency unblinding. As requested by the investigator or sub-investigator the emergency unblinding call center will provide the information to him/her

promptly and report unblinding to the sponsor. The emergency unblinding call center will make a record promptly however, the investigator or sub-investigator must enter the toxicity grade of the adverse experiences observed, their relation to study drug, the reason thereof, etc., in the medical chart etc., before unblinding is performed.

Additionally, the investigator must go into the IVRS system and perform the unblind in the IVRS system to update drug disposition. In the event that the emergency unblinding call center is not available for a given site in this trial, IVRS/IWRS should be used for emergency unblinding in the event that this is required for subject safety.

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

In the event that unblinding has occurred, the circumstances around the unblinding (eg, date and reason) must be documented promptly, and the Sponsor Clinical Director notified as soon as possible. Once an emergency unblinding has taken place, the principal investigator, site personnel, and Sponsor personnel are unblinded so that appropriate follow-up medical care can be provided to the subject.

At the end of the trial, unblinding logs are to be returned to the Sponsor or designee.

7.1.4.3 Calibration of Critical Equipment

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

Critical Equipment for this trial includes:

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

See protocol-specified guidance in the Administrative Binder, Procedures 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

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

Approximately 28 days prior to randomization, potential subjects will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5.1. Screening procedures may be repeated after consultation with the Sponsor.

Written consent must be obtained prior to performing any protocol specific procedure. Screening procedures (i.e., vital signs and full physical exam) and results of a test performed prior to the subject signing consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame. Screening procedures are to be completed within 28 days prior to the first dose of trial treatment except for the following:

- Laboratory tests are to be performed within 10 days prior to the first dose of trial treatment.
- For women of reproductive potential, a urine pregnancy test will be performed within 72 hours prior to first dose of trial treatment. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test, performed by the local study site laboratory, will be required.
- Tumor imaging must be performed within 30 days prior to the first dose of trial treatment.

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

7.1.5.2 Treatment Phase

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

7.1.5.3 Post-Treatment

Visit requirements are outlined in Section 6.0 - Trial Flow Chart. Specific procedure-related details are provided above in Section 7.1 - Trial Procedures. Subjects will be followed for up to 2 years. If the subject experienced a CR, PR, or SD during the Treatment Phase on pembrolizumab, and then experiences PD at any time during that two year follow-up period, he/she will be eligible to receive up to 12 months of therapy with pembrolizumab in the Second Course Phase according to the criteria in Section 7.1.5.4. After the Second Course Phase, subjects should be followed for up to two years, with no option for retreatment with pembrolizumab on study.

Subjects who discontinue trial treatment for a reason other than disease progression will **still be considered as on study** and should continue with regularly scheduled assessments (also refer to Section 7.1.2.7.3), including collecting subject information on the start of new antineoplastic therapy, disease progression, and death.

7.1.5.3.1 Safety Follow-up Visit

The mandatory Safety Follow-Up Visit should be conducted approximately 30 days after the last dose of trial treatment or before the initiation of a new antineoplastic treatment, whichever comes first.

All AEs that occur prior to the Safety Follow-up Visit should be recorded. Subjects with an AE of Grade >1 will be further followed until the resolution of the AE to Grade 0-1 or until

the beginning of a new anticancer therapy, whichever occurs first. Serious AEs that occur within 90 days of the end of treatment or before initiation of a new anticancer treatment should also be followed and recorded.

Subjects who are eligible per the requirements in Section 7.1.5.4 for treatment with pembrolizumab during the Second Course Phase (retreatment) may have up to 2 safety follow-up visits, one after the Initial Treatment Phase and the second after the Second Course Phase. Subjects who are eligible per the requirements in Section 7.1.5.5 for treatment with pembrolizumab during the Crossover Phase may have up to 2 safety follow- up visits, one after the Crossover Phase and another after the Second Course Phase.

7.1.5.3.2 Follow-up Visits

Subjects who discontinue trial treatment for a reason other than disease progression will move into the Follow-Up Phase and should be assessed every 6 weeks after the Safety Follow-up Visit to monitor disease status. Every effort should be made to collect information regarding disease status until the start of new anti-cancer therapy, disease progression, death, or end of trial. Information regarding post-trial anticancer treatment will be collected if new treatment is initiated.

Subjects who are eligible to receive retreatment with pembrolizumab according to the criteria in Section 7.1.5.4 will move from the Follow-Up Phase to the Second Course Phase when they experience disease progression. Details are provided in the Trial Flow Chart (Section 6) for retreatment with pembrolizumab.

7.1.5.3.3 Survival Follow-up

Once a subject experiences PD or starts a new anti-cancer therapy, the subject moves into the Survival Follow-Up Phase and should be contacted by telephone approximately every 12 weeks to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first. Post-study treatments and the subject's response to them will also be collected.

7.1.5.4 Survival Status

To ensure current and complete survival data is available at the time of any database lock, updated survival status may be requested during the course of the study by the Sponsor. For example, updated survival status may be requested prior to, but not limited to, an eDMC review. Upon Sponsor notification, all participants who do not/will not have a scheduled study visit or study contact during the sponsor-defined time period will be contacted for their survival status (excluding participants who have a previously recorded death event in the collection tool).

7.1.5.5 Second Course Phase (Retreatment Period)

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

All subjects who stop trial treatment with SD or better may be eligible for up to an additional 17 cycles (approximately 1 year) of pembrolizumab treatment if they progress after stopping trial treatment from the initial treatment phase. This retreatment is termed the Second Course

Phase of this trial and is only available if the trial remains open and the subject meets the following conditions:

Either

- Stopped initial treatment with trial treatment after attaining an investigator-determined confirmed CR based on RECIST 1.1, and
  - Was treated with at least 8 cycles of trial treatment before discontinuing treatment, and
  - Received at least 2 treatments with pembrolizumab/placebo beyond the date when the initial CR was declared

OR

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

AND

- Experienced an investigator-determined radiographic disease progression by RECIST 1.1 after stopping initial treatment, and
  - Upon unblinding at the time of centrally verified disease progression were found to have received pembrolizumab, and
  - No new anticancer treatment was administered after the last dose of trial treatment, and
  - The subject meets all of the safety parameters listed in the inclusion criteria and none of the safety parameters listed in the exclusion criteria, and the trial is ongoing.

An objective response or progression of disease that occurs during the Second Course Phase for a subject will not be counted as an event for the primary analysis of either endpoint in this trial.

7.1.5.6 Crossover for Subjects With Documented Disease Progression Who Received Placebo

Subjects who are randomized into the placebo with chemotherapy arm will have the opportunity to crossover to receive pembrolizumab monotherapy after they experience disease progression on placebo with chemotherapy and are unblinded. Subjects who permanently discontinue chemotherapy due to an AE, withdrawn consent, or any reason other than progressive disease, will not be eligible for crossover. Crossover subjects must not initiate treatment with pembrolizumab monotherapy any earlier than 21 days after their last dose of chemotherapy regardless of the time of progression.

Crossover Qualifications:

Subjects who received placebo will be considered for crossover to pembrolizumab monotherapy after documented, progressive disease assessed based on RECIST 1.1 by BICR. Crossover is optional and is at the discretion of the Investigator (with the Sponsor's agreement). Subjects who meet the following criteria are eligible for crossover:

- Documented verification of progressive disease by BICR
- Adverse events (except alopecia) due to therapy must have improved to CTCAE (Version 4.0) Grade ≤1
- If a subject is unstable as a result of a new or progressing brain metastasis(es), the subject will not be eligible for crossover.
- ECOG Performance Status 0-1
- Subject has not received any systemic anti-cancer therapies other than the chemotherapy administered during the treatment phase.
- If required, completed palliative radiotherapy (30Gy or less) ≥ 7 days before the first dose of crossover trial treatment.
- If progressive disease is centrally verified but subject does not qualify for Crossover, unblinding may be considered after consulting with Sponsor.

7.1.5.7 Crossover Assessments and Procedures

Crossover subjects must not initiate treatment with pembrolizumab monotherapy any earlier than 21 days after their last dose of chemotherapy regardless of the time of progression. The subject will then start the crossover phase as outlined in Crossover Flow Chart in Section 6.3. Screening procedures need to be completed within 28 days of centrally verified progressive disease (or up to 42 days from last dose if recovering from adverse event). All procedures and assessments completed at the time of withdrawal from the main study may be used as appropriate for the start of the Crossover Phase of the study. The tumor image used to determine progressive disease can be used as the new baseline image for the Crossover phase if 1) 30 days prior to receiving the first dose of pembrolizumab monotherapy and 2) No study treatment between the image and first dose of pembrolizumab monotherapy, otherwise a new baseline image must be performed prior to pembrolizumab monotherapy treatment. Subjects who crossover and then achieve a CR per RECIST 1.1 have the option to hold pembrolizumab while continuing in the trial. Additional details are provided in Second Course Phase Section 7.1.5.4.

7.2 Assessing and Recording Adverse Events

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

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

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

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

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

All adverse events that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure. From the time of treatment allocation/randomization through 30 days following cessation of treatment, all adverse events must be reported by the investigator. Such events will be recorded at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in section 7.2.3.1. The investigator will make every attempt to follow all subjects with non-serious adverse events for outcome.

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

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

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

For purposes of this trial, an overdose will be defined as any dose exceeding the prescribed dose for pembrolizumab by ≥1000 mg (5 times the dose).. No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, pembrolizumab should be discontinued and the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

If an adverse event(s) is associated with ("results from") the overdose of Sponsor's product 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 180 days after last dose of chemotherapeutic agents or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, must be reported by the investigator. All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

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

7.2.3 Immediate Reporting of Adverse Events to the Sponsor

7.2.3.1 Serious Adverse Events

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

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

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

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

Refer to [Table 10] for additional details regarding each of the above criteria.

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

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

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

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

7.2.3.2 Events of Clinical Interest

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

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

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

Events of clinical interest for this trial include:

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

than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

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

7.2.3.3 Protocol-Specific Exceptions to Serious Adverse Event Reporting

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

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

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

7.2.4 Evaluating Adverse Events

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

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

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 10 Evaluating Adverse Events

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

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

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

7.2.5 Sponsor Responsibility for Reporting Adverse Events

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

7.3 TRIAL GOVERNANCE AND OVERSIGHT

7.3.1 Scientific Advisory Committee

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

7.3.2 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 Sponsor per the DMC Charter regarding steps to ensure both subject safety and the continued ethical integrity of the trial. Also, the DMC will review interim trial results, consider the overall risk and benefit to trial participants (see Section 8.7 - Interim Analyses) and recommend to the Sponsor 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. The DMC will also make recommendations to the Sponsor executive committee and/or protocol team regarding steps to ensure both subject safety and the continued ethical integrity of the trial.

A DMC recommendation will be communicated to the Sponsor as agreed to in the DMC Charter.

8.0 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, changes made to primary and/or key secondary hypotheses, or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with ICH Guideline E-9). Changes to exploratory or other non-confirmatory analyses made after the protocol has been finalized, but prior to the conduct of any analysis, will be documented in a supplemental SAP (sSAP) and referenced in the Clinical

Study Report (CSR) for the study. Post hoc exploratory analyses will be clearly identified in the CSR.

8.1 Statistical Analysis Plan Summary

Key elements of the statistical analysis plan are summarized below; the comprehensive plan is provided in Sections 8.2 through 8.12.

Study Design Overview	A Phase 3 Study of Platinum+ Pemetrexed Chemotherapy with or without Pembrolizumab (MK-3475) in First Line Metastatic Nonsquamous Non-small Cell Lung Cancer Subjects (KEYNOTE-189)
Treatment Assignment	Approximately 570 subjects will be randomized in a 2:1 ratio to receive pembrolizumab or saline placebo in combination with pemetrexed/platinum. Stratification factors are in Section 5.4. This is a randomized double-blinded study.
Analysis Populations	Efficacy: Intention to Treat (ITT) Safety: All Subjects as Treated (ASaT)
Primary Endpoints/Hypotheses	. Progression-free Survival (PFS) per RECIST 1.1 assessed by BICR Overall Survival (OS)
Statistical Methods for Key Efficacy Analyses	The primary hypotheses for PFS and OS will be evaluated by comparing pembrolizumab to saline placebo in combination with pemetrexed/platinum using a stratified Log-rank test. The HR will be estimated using a stratified Cox regression model. Event rates over time will be estimated within each treatment group using the Kaplan-Meier method.
Statistical Methods for Key Safety Analyses	The analysis of safety results will follow a tiered approach. There are no Tier 1 safety parameters in this trial. All safety parameters are considered either 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. The between-treatment difference will be analyzed using the Miettinen and Nurminen method. In the primary safety comparison, subjects who crossover to pembrolizumab are censored at time of crossover (ie, AEs occurring during treatment with pembrolizumab are excluded for control-arm subjects). An exploratory safety analysis will be conducted for the crossover population including all safety events starting from the date of first dose of pembrolizumab.
Interim Analyses	Two interim analyses are planned in this study. Results will be reviewed by an external data monitoring committee. Details are provided in Section 8.7. . Interim analysis 1 (IA1) o Timing: To be performed after target number of PFS events (~370) are observed o Purpose: To demonstrate superiority of pembrolizumab in combination with pemetrexed/platinum in PFS and OS. ORR will be tested after superiority of pembrolizumab in combination with pemetrexed/platinum is demonstrated in PFS and OS. Interim analysis 2 (IA2) o Timing: To be performed after ~468 PFS events are observed

	o Purpose: To demonstrate superiority of pembrolizumab in combination with pemetrexed/platinum in PFS and OS.
Final Analysis	Final analysis (FA) o Timing: To be performed after target number of deaths (~416) are observed o Purpose: To demonstrate superiority of pembrolizumab in combination with pemetrexed/platinum in OS.
Multiplicity	The overall Type I error rate for each endpoint in the group sequential tests is strictly controlled at 2.5% (one-sided); for both PFS and OS, this is based on the Lan-DeMets O'Brien-Fleming spending function (see Section 8.7 for details). Between the endpoints, the type I error is controlled by the following rollover rule. The total type I error allocated to PFS (0.0095) is subject to rollover to OS if the PFS test is positive. The type I error allocated to OS (0.0155) is subject to rollover to PFS if the OS test is positive. Furthermore, the total type I error (0.025) is subject to rollover to ORR at IA1 if the PFS and OS tests are both positive.
Sample Size and Power	Enrollment of 570 subjects is assumed to occur over 12 months at 2:1 ratio between the experimental and control groups. The actual enrollment is 616 subjects within 13 months. With 370 PFS events at IA1, the study has ~72% power for detecting a PFS HR of 0.7 at 0.0095 (one-sided) and ~84% power for detecting a HR of 0.7 at 0.025 (one-sided). With 468 PFS events at IA2, the study has ~90% power for detecting a HR of 0.7 at 0.0095 (one-sided) and ~96% power for detecting a HR of 0.7 at 0.025 (one-sided). The duration of PFS in the control group is assumed to follow an exponential distribution with a median of 6.5 months based on historical data. The assumed follow-up time after last patient enrolled is 13 months for IA2. An exponential dropout rate of 0.35% per month is assumed. With 242 deaths at IA1, the study has ~37% power for detecting an OS HR of 0.7 at 0.0155 (one-sided) and ~47% power for detecting a HR of 0.7 at 0.025 (one-sided) when the PFS test is significant. With 332 deaths at IA2, the study has ~73% power for detecting a HR of 0.7 at 0.0155 (one-sided) and ~80% power for detecting a HR of 0.7 at 0.025 (one-sided) when the PFS test is significant. With 416 deaths at FA, the study has ~90% power for detecting a HR of 0.7 at 0.0155 (one-sided) and ~93% power for detecting a HR of 0.7 at 0.025 (one-sided) when the PFS test is significant. The duration of OS in the control group is assumed to follow an exponential distribution with a median of 13 months based on historical data. The exponential dropout rate assumed for OS is 0.1% per month.

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

This trial is double blinded with a crossover phase. At the time of documented progression, subjects will have treatment assignment unblinded and be able to continue therapy in the Crossover Phase, please refer to Section 2.1 Trial Design for details. In addition, independent

central radiologist(s) will perform the central imaging review without knowledge of treatment 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 data management personnel, 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 or the unblinded Sponsor statistician.

An external data monitoring committee (eDMC) will be convened to review accumulating safety to provide an opportunity to terminate the study early if there are concerns regarding safety. The eDMC will also review the unblinded efficacy results at the planned interim analysis. The eDMC responsibilities and review schedules will be outlined in the eDMC charter. The recommendation of the eDMC will be communicated to an executive oversight committee of the Sponsor and, in the event of a recommendation to halt the trial early due to safety concerns, to the appropriate regulatory agencies. 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.

Limited numbers of additional Sponsor personnel may be unblinded, if required, in order to act on the recommendations of the eDMC. The extent to which individuals are unblinded with respect to the results will be documented. Additional logistical details, revisions to the above plan and data monitoring guidance will be provided in the eDMC Charter.

8.3 Hypotheses/Estimation

Objectives and hypotheses of the study are stated in Section 3.0.

8.4 Analysis Endpoints

8.4.1 Efficacy Endpoints

Primary

Progression-free survival (PFS) – RECIST 1.1 assessed by BICR

PFS is defined as the time from randomization to the first documented disease progression per RECIST 1.1 based on BICR or death due to any cause, whichever occurs first. See Section 8.6.1 for definition of censoring.

Overall Survival

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

Secondary

Objective Response Rate (ORR) – RECIST 1.1 assessed by BICR

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

Duration of Response (DOR) – RECIST 1.1 assessed by BICR

For subjects who demonstrated confirmed CR or PR, DOR is defined as the time from first documented evidence of CR or PR until disease progression or death. DOR for subjects who have not progressed or died at the time of analysis will be censored at the date of their last tumor assessment.

8.4.2 Safety Endpoints

Safety measurements are described in Section 7.

8.5 Analysis Populations

8.5.1 Efficacy Analysis Populations

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

If an unexpectedly large number of randomized subjects are not treated, analyses may be performed using the Full Analysis Set (FAS), including all randomized subjects who received at least 1 dose of study treatment and did not have a major protocol violation.

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

Extension Study

After the sample size required for the global study is reached, the study will continue to randomize subjects in Japan until the sample size for the Japanese subjects meets the target. The Japanese subjects randomized in the extension study will not be included in the above primary efficacy analysis population. The ITT Japanese subjects as well as the entire ITT population consisting of the primary efficacy population and subjects randomized in the extension will be analyzed separately per local regulatory requirement.

8.5.2 Safety Analysis Populations

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

the treatment group corresponding to the study treatment actually received. Any subject who receives the incorrect study medication for one cycle but receives the correct treatment for all other cycles will be analyzed according to the correct treatment group and a narrative will be provided for any events that occur during the cycle for which the subject is incorrectly dosed.

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

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

Extension Study

The Japanese subjects randomized and treated in the extension study will not be included in the above primary safety analysis population. The ASaT Japanese subjects as well as the entire ASaT population consisting of the primary safety population and subjects randomized and treated will be analyzed per local regulatory requirements.

8.6 Statistical Methods

8.6.1 Statistical Methods for Efficacy Analyses

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

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

All statistical tests, unless otherwise specified, will be stratified for treatment and stratification factors.

8.6.1.1 Progression-free Survival (PFS)

The non-parametric 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 (based on the stratification factors defined in Section 5.4). A stratified Cox proportional hazard model with Efron's method of tie handling will be used to assess the magnitude of the treatment difference (ie, 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 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, PD can occur any time in the time interval between the last assessment where PD was not documented and the assessment when PD is documented. For the primary analysis, for the subjects who have PD, the true date of disease progression will be approximated by the date of the first assessment at which PD is objectively documented per RECIST 1.1 by BICR, regardless of discontinuation of study

drug. Death is always considered as a confirmed PD event. Sensitivity analyses will be performed for comparison of PFS based on investigator's assessment.

In order to evaluate the robustness of the PFS endpoint per RECIST 1.1 by central imaging vendor, we will perform 2 sensitivity analyses with different sets 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 an anticancer treatment subsequent to discontinuation of study-specified treatments, whichever occurs later, to be a PD event for subjects without documented PD or death. The censoring rules for primary and sensitivity analyses are summarized in [Table 11]. In case there is an imbalance between the treatment groups on disease assessment schedules or censoring patterns, we will perform an additional PFS sensitivity analysis using time from randomization to scheduled tumor assessment time instead of actual tumor assessment.

Table 11 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

In case the proportional hazards assumption is not valid, Restricted Mean Survival Time (RMST) method may be conducted for PFS to account for the possible non-proportional hazards effect.

An exploratory analysis of PFS2, defined as the time from randomization to second/subsequent disease progression after initiation of new anti-cancer therapy, or death from any cause, whichever first, will be carried out. Patients alive and for whom a second objective disease progression has not been observed will be censored at the last time known to be alive and without second objective disease progression.

Further details of sensitivity analyses will be described in sSAP as needed.

8.6.1.2 Overall Survival (OS)

The non-parametric 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 (based on the

stratification factor defined in Section 5.4). A stratified Cox proportional hazard model with Efron's method of tie handling will be used to assess the magnitude of the treatment difference (ie, 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 stratification factors used for randomization (See Section 5.4) will be applied to both the stratified log-rank test and the stratified Cox model. Restricted Mean Survival Time (RMST) method may be conducted for OS to account for the possible non-proportional hazards effect.

Since subjects in the control arm are allowed to switch to the pembrolizumab treatment after progressive disease, adjustment for the effect of crossover on OS may be performed based on recognized methods, eg, a two-stage method or the Rank Preserving Structural Failure Time (RPSFT) model proposed by Robins and Tsiatis [43], based on an examination of the appropriateness of the data to the assumptions required by the methods.

Further details of sensitivity analyses will be described in sSAP as needed.

8.6.1.3 Objective Response Rate (ORR) and Duration of Response (DOR)

Stratified Miettinen and Nurminen's method will be used for comparison of the ORR between 2 treatment groups. The difference in ORR and its 95% confidence interval from the stratified Miettinen and Nurminen's method with strata weighting by sample size with a single treatment covariate will be reported. The stratification factors used for randomization (See Section 5.4) will be applied to the analysis.

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

[Table 12] summarizes the primary analysis approach for primary and key secondary efficacy endpoints. Sensitivity analysis methods are described above for each endpoint as applicable.

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

Table 12 Analysis Strategy for Key Efficacy Endpoints

Endpoint/Variable (Description, Time Point)	Statistical Method†	Analysis Population	Missing Data Approach
Primary Endpoints			
PFS per RECIST 1.1 by central imaging vendor	Test: Stratified Log-rank test to assess the treatment difference Estimation: Stratified Cox model with Efron's tie handling method to assess the magnitude of treatment difference	ITT	• Primary censoring rule • Sensitivity analysis 1 • Sensitivity analysis 2
OS	Test: Stratified Log-rank test to assess the treatment difference Estimation: Stratified Cox model with Efron's tie handling method to assess the magnitude of treatment difference	ITT	Model based (censored at last known alive date)
Secondary Endpoint			
ORR per RECIST 1.1 by central imaging vendor	Stratified M&N method with sample size weights††	ITT	Subjects without assessments are considered non-responders and conservatively included in denominator

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

†† Miettinen and Nurminen method

8.6.2 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, etc.

Adverse Events

Adverse events (AEs) will be coded using the standard MedDRA and grouped system organ class. Adverse events (AEs) will be graded by the investigator according to the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0.

Tiered Approach

The analysis of safety results will follow a tiered approach [Table 13]. The tiers differ with respect to the analyses that will be performed. "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 events. 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) 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 event s 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, that are not pre-specified as Tier-1 endpoints 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.

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 (1985), an unconditional, asymptotic method.

Table 13 Analysis Strategy for Safety Parameters

Safety Tier	Safety Endpoint[†]	95% CI for Treatment Comparison	Descriptive Statistics
Tier 2	Any AE	X	X
	Any Serious AE	X	X
	Any Grade 3-5 AE	X	X
	Any Drug-Related AE	X	X
	Any Serious and Drug-Related AE	X	X
	Any Grade 3-5 and Drug-Related AE	X	X
	Dose Modification due to AE	X	X
	Discontinuation due to AE	X	X
	Death		
	Specific AEs, SOCs, or PDLCs[‡] (incidence ≥4 of subjects in one of the treatment groups)	X	X
Tier 3	Specific AEs, SOCs or PDLCs[‡] (incidence <4 of subjects in all of the treatment groups)		X
	Change from Baseline Results (Labs, ECGs, Vital Signs)		X

8.6.3 Summaries of Demographic and Baseline Characteristics and Other Analysis

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

8.7 Interim Analyses

Two interim efficacy analyses are planned in addition to the final analysis.

- The first interim analysis (IA1) will evaluate PFS and OS. It will be performed after enrollment is complete and approximately 370 PFS events have been observed, approximately 19 months after first patient enrolled. It is estimated that approximately 242 deaths will be observed. ORR will be tested at this interim analysis if both the PFS and OS test results are significant.

- The second interim analysis (IA2) is the final analysis for PFS and will be performed after approximately 468 PFS events have been observed, approximately 26 months after first patient enrolled. An interim analysis of OS will be performed; it is estimated that approximately 332 deaths will be observed.
- The final analysis (FA) will evaluate OS only and will be performed after approximately 416 deaths have been observed. It is estimated that this will occur approximately 35 months after enrollment begins.

The analyses planned, endpoints evaluated and drivers of the timing are summarized in [Table 14].

Table 14 Analyses Planned, Endpoints Evaluated, and Drivers of Timing

Analysis	Endpoint(s)	Timing
IA1	PFS; OS; ORR if both PFS and OS are positive	~370 PFS events (~242 OS events expected at this time)
IA2	PFS; OS	~468 PFS events (~332 OS events expected at this time)
FA	OS	~416 OS events

Decisions to stop the trial early will be based on DMC recommendations with review by the Executive Oversight Committee.

Type I error control for the efficacy analyses as well as efficacy bounds are described in the next section.

8.8 Multiplicity

The trial uses the graphical method of Maurer and Bretz [44] to provide strong multiplicity control for multiple hypotheses as well as interim analyses.

Figure 2 shows the initial one-sided α-allocation for each hypothesis in the ellipse representing the hypothesis. The weights for reallocation from each hypothesis to the others are represented in the boxes on the lines connecting hypotheses. This is further explained below.

See Figure 2 for the type I error reallocation strategy for endpoints PFS, OS, and ORR.

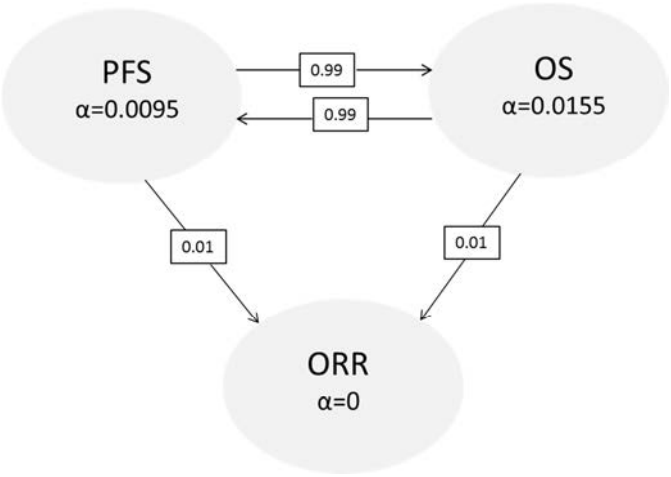

Figure 2 Type I Error Reallocation Strategy

PFS

PFS hypothesis will be tested at α=0.0095. When OS test is significant, the PFS hypothesis may be tested at α=0.025 (re-allocated α). The Lan-DeMets O'Brien-Fleming spending function was used to control the type I error in the interim analysis. [Table 15] below demonstrates the bounds and boundary properties for PFS hypothesis testing. The table will be updated using the actual number of PFS events at the interim and final PFS analyses.

Table 15 Boundary properties for planned analyses of PFS based on potential alpha-levels to be used for testing

Analysis	Value	α=0.0095	α=0.025
IA 1: 79%	Z	2.6946	2.2676
N: 616	p (1-sided)	0.0035	0.0117
Events: 370	HR at bound	0.7427	0.7790
Month: 19.2	P(Cross) if HR=1	0.0035	0.0117
	P(Cross) if HR=0.7	0.7160	0.8439
IA2*	Z	2.3895	2.0222
N: 616	p (1-sided)	0.0084	0.0216
Events: 468	HR at bound	0.7910	0.8204
Month: 26	P(Cross) if HR=1	0.0095	0.0250
	P(Cross) if HR=0.7	0.9040	0.9550

*The final analysis of PFS will be performed at IA2.

If the OS superiority null hypotheses are rejected at an interim or final analysis, each PFS interim analysis test may be compared to its updated rejection boundary for formal testing.

OS

The OS hypothesis will be tested at α=0.0155. When PFS test is significant, the OS hypothesis may be tested at α=0.025 (re-allocated α). [Table 16] demonstrates the bounds and boundary properties for OS hypothesis testing. The HR of OS between the experimental group and control group is assumed to be 0.7. The table will be updated using the actual number of OS events at the interim and final OS analyses. The Lan-DeMets O'Brien-Fleming spending function was used to derive the design in α columns.

Table 16 Boundary properties for planned analyses of OS

Analysis	Value	α=0.0155	α=0.025
IA 1: 58%	Z	2.9715	2.7215
N: 616	p (1-sided)	0.0015	0.0032
Events: 242	HR at bound	0.6662	0.6893
Month: 19.3	P(Cross) if HR=1	0.0015	0.0032
	P(Cross) if HR=0.7	0.3711	0.4695
IA 2: 80%	Z	2.4926	2.2831
N: 616	p (1-sided)	0.0063	0.0112
Events: 332	HR at bound	0.7482	0.7666
Month: 26.2	P(Cross) if HR=1	0.0068	0.0122
	P(Cross) if HR=0.7	0.7332	0.7991
Final	Z	2.2155	2.0300
N: 616	p (1-sided)	0.0134	0.0212
Events: 416	HR at bound	0.7940	0.8095
Month: 35	P(Cross) if HR=1	0.0155	0.0250
	P(Cross) if HR=0.7	0.9000	0.9300

A sensitivity analysis for OS will be pre-specified in the supplemental statistical analysis plan to account for any multiplicity concerns raised by not formally testing the OS null hypothesis such as DMC requests. This analysis will be performed if requested by regulators. However, there is no plan to do formal testing at these analyses or to declare a positive efficacy finding based on these results.

If the PFS superiority null hypotheses are rejected at any interim analyses, each OS interim and final analysis test may be compared to its updated rejection boundary for formal testing.

ORR

When both PFS and OS tests are significant, α=0.025 will be allocated to the ORR test. If the OS test does not achieve statistical significance at IA1, the p value of the ORR test from IA1 will be compared to 2.5% if the null hypotheses for PFS and OS are rejected at a later time.

8.9 Sample Size and Power Calculations

This trial is well-powered for the primary and key secondary endpoints. Enrollment of 570 subjects is assumed to occur over 12 months at 2:1 ratio between the experimental and control groups. The actual enrollment is 616 subjects within 13 months. With 370 PFS events at IA1, the study has ~72% power for detecting a HR of 0.7 at 0.0095 (one-sided) and ~84% power for detecting a HR of 0.7 at 0.025 (one-sided). With 468 PFS events at IA2, the study has ~90% power for detecting a HR of 0.7 at 0.0095 (one-sided) and ~96% power for detecting a HR of 0.7 at 0.025 (one-sided). The duration of PFS in the control group is assumed to follow an exponential distribution with a median of 6.5 months based on historical data. The assumed follow-up time after last patient enrolled is 13 months for IA2. An exponential dropout rate of 0.35% per month is assumed.

With 242 deaths at IA1, the study has ~37% power for detecting a HR of 0.7 at 0.0155 (one-sided) and ~47% power for detecting a HR of 0.7 at 0.025 (one-sided) when the PFS test is significant. With 332 deaths at IA2, the study has ~73% power for detecting a HR of 0.7 at 0.0155 (one-sided) and ~80% power for detecting a HR of 0.7 at 0.025 (one-sided) when the PFS test is significant. With 416 deaths at FA, the study has ~90% power for detecting a HR of 0.7 at 0.0155 (one-sided) and ~93% power for detecting a HR of 0.7 at 0.025 (one-sided) when the PFS test is significant. The duration of OS in the control group is assumed to follow an exponential distribution with a median of 13 months based on historical data. The exponential dropout rate assumed for OS is 0.1% per month.

The sample size of 616 yields 89% (α=0.025) power to detect an ORR difference from an underlying 45% response rate in the control group to 60% in the experimental group, when both PFS and OS tests are significant. The approximate treatment difference required to reach the bound (Δ ORR) is 0.0575.

Power and interim analysis calculations were performed using EAST 5 and the gsDesign R package.

Extension Study

After the enrollment for the global study has completed, the study will continue to randomize subjects in a 2:1 ratio into the pembrolizumab/pemetrexed/platinum arm or saline placebo/pemetrexed/platinum arm in Japan until the sample size for the Japanese subjects

reaches approximately 30. The sample size for the overall Japanese subjects is projected to be approximately 40. Japanese subjects randomized after completion of enrollment in the global study will not be included in the analysis of the global study.

8.10 Subgroup Analyses and Effect of Baseline Factors

To determine whether the treatment effect is consistent across various subgroups, the between-group treatment effect for OS, PFS, and ORR (with a nominal 95% CI) will be estimated and plotted within each category of the following classification variables (a subgroup will not be analyzed if it includes <10% of the ITT population):

- Age category (<65, ≥65 years)
- ECOG Performance Scale (0, 1)
- Sex (female, male)
- Race (white, non-white)
- Geographic region (US, Ex US)
- Geographic region (EU, Ex EU)
- Smoking status (never, former/current)
- Brain metastasis status at baseline (yes, no)
- PD-L1 expression (unknown, TPS <1%, or TPS ≥1%)
- PD-L1 expression (unknown, TPS <50%, or TPS ≥50%)
- PD-L1 expression (unknown, TPS <1%, 1%≤TPS≤49%, or TPS ≥50%)
- Platinum chemotherapy (cisplatin, carboplatin)

8.11 Extent of Exposure

The extent of exposure will be summarized as duration of treatment in cycles.

9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.1 Investigational Product

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

Clinical Supplies will be provided by the Sponsor as summarized in [Table 17].

Table 17 Product Descriptions

Product Name & Potency	Dosage Form
Pembrolizumab 25 mg/mL	Solution for infusion
Pemetrexed* 500 mg/vial	Lyophilized powder for infusion
Carboplatin 10 mg/mL	Solution for infusion
Cisplatin 1 mg/mL	Solution for infusion
*Pemetrexed disodium	

All other supplies not indicated in [Table 17] 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, 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.

All supplies will be provided open label. Pembrolizumab will be provided as non-kitted single vials or as single vials in a kit box. Pemetrexed will be supplied as a single vial. All other products will be provided as a kit with a single vial.

9.3 Clinical Supplies Disclosure

This trial is blinded but provided open label; therefore, an unblinded pharmacist or qualified trial site personnel will be used to blind supplies. Treatment identity (name, strength or potency) is included in the label text; random code/disclosure envelopes or lists are not provided.

The emergency unblinding call center will use the treatment/randomization schedule for the trial to unblind subjects and to unmask treatment identity. In the event that the emergency unblinding call center is not available for a given site in this trial, the central electronic treatment allocation/randomization system (IVRS/IWRS) should be used in order to unblind subjects and to unmask treatment identity. The Sponsor will not provide random code/disclosure envelopes or lists with the clinical supplies.

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

In the event that unblinding has occurred, the circumstances around the unblinding (e.g., date and reason) must be documented promptly, and the Sponsor Clinical Director notified as soon as possible. Once an emergency unblinding has taken place, the principal investigator,

site personnel, and Sponsor personnel are unblinded so that appropriate follow-up medical care can be provided to the subject.

9.4 Storage and Handling Requirements

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

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

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

9.5 Discard/Destruction/Returns and Reconciliation

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

9.6 Standard Policies

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

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

10.1 Confidentiality

10.1.1 Confidentiality of Data

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

10.1.2 Confidentiality of Subject Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), IRB/ERC, or regulatory authority representatives may consult and/or copy trial documents in order to verify worksheet/case report form data. By signing the consent form, the subject

agrees to this process. If trial documents will be photocopied during the process of verifying worksheet/case report form information, the subject will be identified by unique code only; full names/initials will be masked prior to transmission to the Sponsor.

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

10.1.3 Confidentiality of Investigator Information

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

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

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

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

10.1.4 Confidentiality of IRB/IEC Information

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

10.2 Compliance with Financial Disclosure Requirements

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

The investigator/subinvestigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor to

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

10.3 Compliance with Law, Audit and Debarment

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

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

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

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

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

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

The investigator must maintain copies of all documentation and records relating to the conduct of the trial in compliance with all applicable legal and regulatory requirements. This documentation includes, but is not limited to, the protocol, worksheets/case report forms, advertising for subject participation, adverse event reports, subject source data, correspondence with regulatory authorities and IRBs/ERCs, consent forms, investigator's curricula vitae, monitor visit logs, laboratory reference ranges, laboratory certification or quality control procedures and laboratory director curriculum vitae. By signing this protocol,

the investigator agrees that documentation shall be retained until at least 2 years after the last approval of a marketing application in an ICH region or until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. Because the clinical development and marketing application process is variable, it is anticipated that the retention period can be up to 15 years or longer after protocol database lock. The Sponsor will determine the minimum retention period and notify the investigator when documents may be destroyed. The Sponsor will determine the minimum retention period and upon request, will provide guidance to the investigator when documents no longer need to be retained. The sponsor also recognizes that documents may need to be retained for a longer period if required by local regulatory requirements. All trial documents shall be made available if required by relevant regulatory authorities. The investigator must consult with and obtain written approval by the Sponsor prior to destroying trial and/or subject files.

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

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

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

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

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

10.4 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the Sponsor of the trial is solely responsible for determining whether the trial and its results are subject to the requirements

for submission to the Clinical Trials Data Bank, http://www.clinicaltrials.gov. Merck, as Sponsor of this trial, will review this protocol and submit the information necessary to fulfill these requirements. Merck entries are not limited to FDAMA/FDAAA mandated trials. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

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

10.5 Quality Management System

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

10.6 Data Management

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

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

10.7 Publications

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

These timelines may be extended for products that are not yet marketed, if additional time is needed for analysis, to protect intellectual property, or to comply with confidentiality agreements with other parties. Authors of the primary results manuscript will be provided

the complete results from the Clinical Study Report, subject to the confidentiality agreement. When a manuscript is submitted to a biomedical journal, the Sponsor's policy is to also include the protocol and statistical analysis plan to facilitate the peer and editorial review of the manuscript. If the manuscript is subsequently accepted for publication, the Sponsor will allow the journal, if it so desires, to post on its website the key sections of the protocol that are relevant to evaluating the trial, specifically those sections describing the trial objectives and hypotheses, the subject inclusion and exclusion criteria, the trial design and procedures, the efficacy and safety measures, the statistical analysis plan, and any amendments relating to those sections. The Sponsor reserves the right to redact proprietary information.

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

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

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

11.0 LIST OF REFERENCES

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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 specimens collected in this trial as outlined in Section 7.1.3.6 – Future Biomedical Research Sample Collection will be used to study various causes for how subjects may respond to a drug/vaccine. Future biomedical research specimen(s) will be stored to provide a resource for future trials conducted by the Sponsor 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 the Sponsor or those working for or with the Sponsor.

3. Summary of Procedures for Future Biomedical Research

a. Subjects for Enrollment

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

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.

c. eCRF Documentation for Future Biomedical Research Specimens

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

d. Future Biomedical Research Specimen Collections

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

4. Confidential Subject Information for Future Biomedical Research

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

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

At the clinical trial site, unique codes will be placed on the Future Biomedical Research specimens 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.

5. Biorepository Specimen Usage

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

6. Withdrawal From Future Biomedical Research

Subjects may withdraw their consent for Future Biomedical Research and 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 to obtain appropriate information to complete specimen withdrawal. Subsequently, the subject's specimens will be removed from the biorepository and be destroyed. Documentation will be sent 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. Retention of Specimens

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

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

8. Data Security

Databases containing specimen information and test results are accessible only to the authorized Sponsor representatives and the designated trial administrator research personnel and/or collaborators. Database user authentication is highly secure, and is accomplished using network security policies and practices based on international standards (e.g., ISO17799) to protect against unauthorized access.

9. Reporting of Future Biomedical Research Data to Subjects

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

If any exploratory results are definitively associated with clinical significance for subjects while the clinical trial is still ongoing, investigators will be contacted with information. After the clinical trial has completed, if any exploratory results are definitively associated with clinical significance, the Sponsor will endeavor to make such results available

through appropriate mechanisms (e.g., scientific publications and/or presentations). Subjects will not be identified by name in any published reports about this study or in any other scientific publication or presentation.

10. Future Biomedical Research Study Population

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

11. Risks Versus Benefits of Future Biomedical Research

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

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

12. Questions

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

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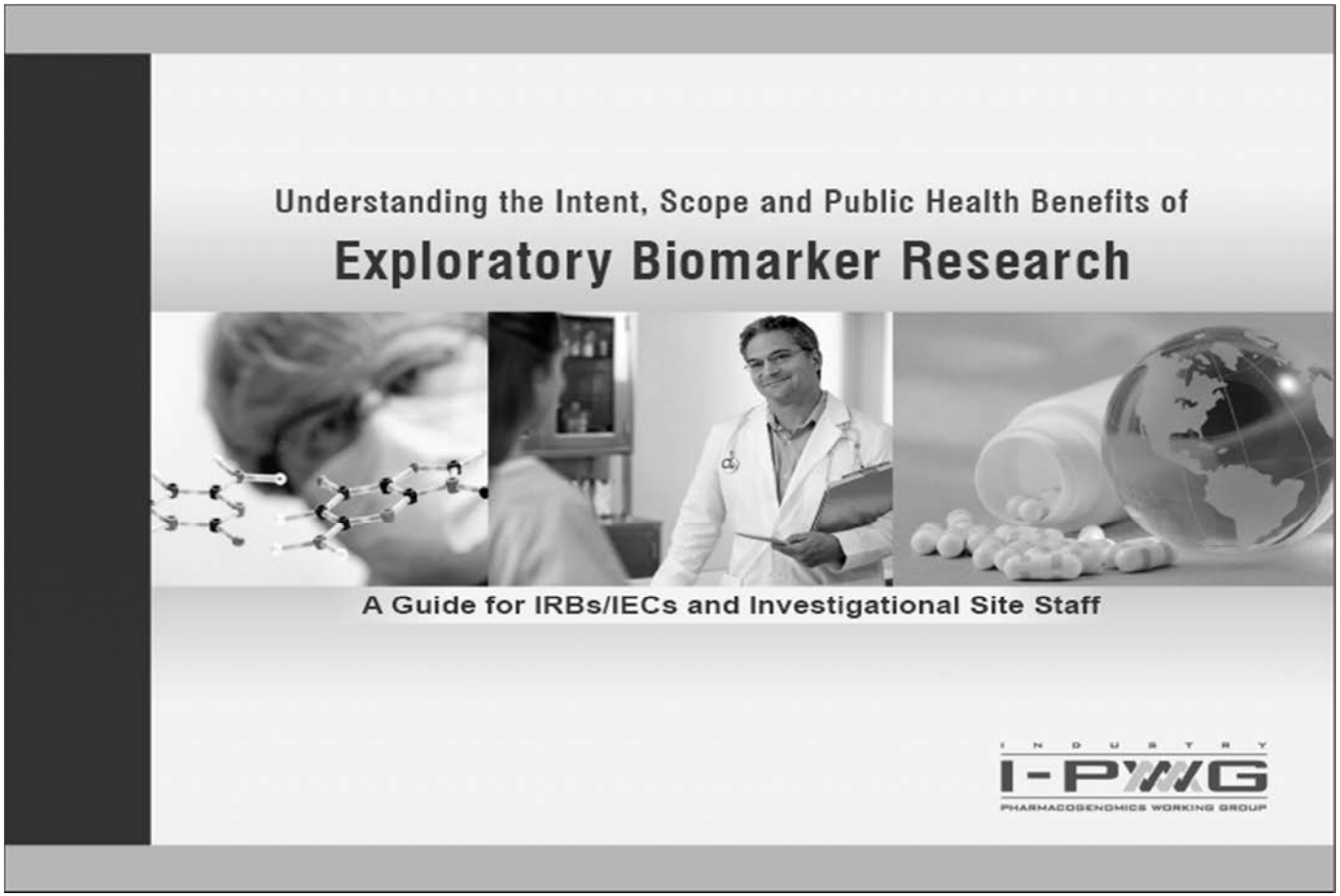
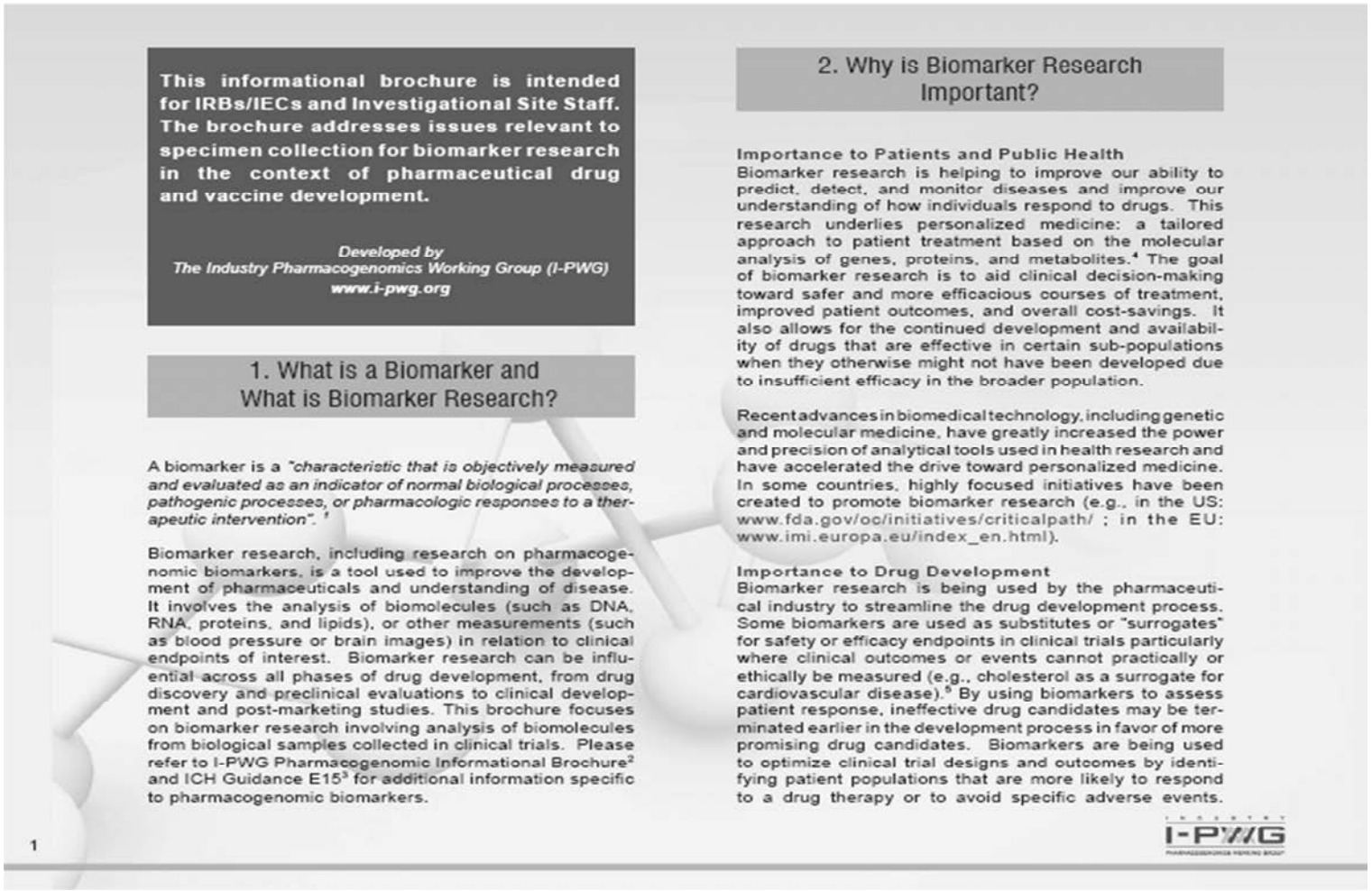
12.3 Understanding the Intent, Scope and Public Health Benefits of Exploratory Biomarker Research: A Guide for IRBs/IECs and Investigational Site Staff





This informational brochure is intended for IRBs/IECs and Investigational Site Staff. The brochure addresses issues relevant to specimen collection for biomarker research in the context of pharmaceutical drug and vaccine development.

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

1. What is a Biomarker and What is Biomarker Research?

A biomarker is a *"characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention".* [1]

Biomarker research, including research on pharmacogenomic biomarkers, is a tool used to improve the development of pharmaceuticals and understanding of disease. It involves the analysis of biomolecules (such as DNA, RNA, proteins, and lipids), or other measurements (such as blood pressure or brain images) in relation to clinical endpoints of interest. Biomarker research can be influential across all phases of drug development, from drug discovery and preclinical evaluations to clinical development and post-marketing studies. This brochure focuses on biomarker research involving analysis of biomolecules from biological samples collected in clinical trials. Please refer to I-PWG Pharmacogenomic Informational Brochure[2] and ICH Guidance E15[3] for additional information specific to pharmacogenomic biomarkers.

2. Why is Biomarker Research Important?

Importance to Patients and Public Health
Biomarker research is helping to improve our ability to predict, detect, and monitor diseases and improve our understanding of how individuals respond to drugs. This research underlies personalized medicine: a tailored approach to patient treatment based on the molecular analysis of genes, proteins, and metabolites.[4] The goal of biomarker research is to aid clinical decision-making toward safer and more efficacious courses of treatment, improved patient outcomes, and overall cost-savings. It also allows for the continued development and availability of drugs that are effective in certain sub-populations when they otherwise might not have been developed due to insufficient efficacy in the broader population.

Recent advances in biomedical technology, including genetic and molecular medicine, have greatly increased the power and precision of analytical tools used in health research and have accelerated the drive toward personalized medicine. In some countries, highly focused initiatives have been created to promote biomarker research (e.g., in the US: www.fda.gov/oc/initiatives/criticalpath/ ; in the EU: www.imi.europa.eu/index_en.html).

Importance to Drug Development
Biomarker research is being used by the pharmaceutical industry to streamline the drug development process. Some biomarkers are used as substitutes or "surrogates" for safety or efficacy endpoints in clinical trials particularly where clinical outcomes or events cannot practically or ethically be measured (e.g., cholesterol as a surrogate for cardiovascular disease).[5] By using biomarkers to assess patient response, ineffective drug candidates may be terminated earlier in the development process in favor of more promising drug candidates. Biomarkers are being used to optimize clinical trial designs and outcomes by identifying patient populations that are more likely to respond to a drug therapy or to avoid specific adverse events.

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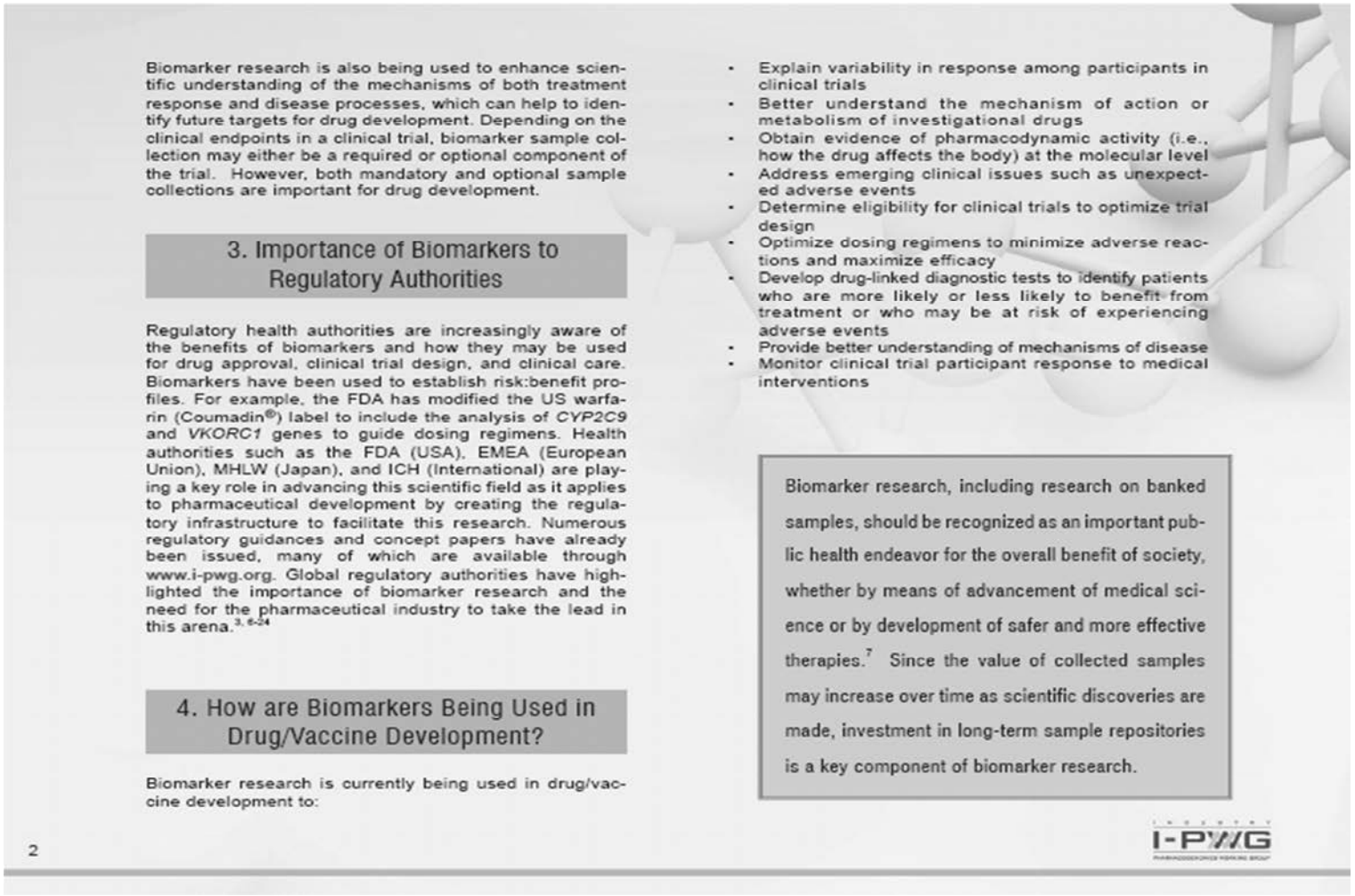
Biomarker research is also being used to enhance scientific understanding of the mechanisms of both treatment response and disease processes, which can help to identify future targets for drug development. Depending on the clinical endpoints in a clinical trial, biomarker sample collection may either be a required or optional component of the trial. However, both mandatory and optional sample collections are important for drug development.
3. Importance of Biomarkers to Regulatory Authorities
Regulatory health authorities are increasingly aware of the benefits of biomarkers and how they may be used for drug approval, clinical trial design, and clinical care. Biomarkers have been used to establish risk:benefit profiles. For example, the FDA has modified the US warfarin (Coumadin®) label to include the analysis of CYP2C9 and VKORC1 genes to guide dosing regimens. Health authorities such as the FDA (USA), EMEA (European Union), MHLW (Japan), and ICH (International) are playing a key role in advancing this scientific field as it applies to pharmaceutical development by creating the regulatory infrastructure to facilitate this research. Numerous regulatory guidances and concept papers have already been issued, many of which are available through www.i-pwg.org. Global regulatory authorities have highlighted the importance of biomarker research and the need for the pharmaceutical industry to take the lead in this arena.[3, 6-24]
4. How are Biomarkers Being Used in Drug/Vaccine Development?
Biomarker research is currently being used in drug/vaccine development to:
Explain variability in response among participants in clinical trials
Better understand the mechanism of action or metabolism of investigational drugs
Obtain evidence of pharmacodynamic activity (i.e., how the drug affects the body) at the molecular level
Address emerging clinical issues such as unexpected adverse events
Determine eligibility for clinical trials to optimize trial design
Optimize dosing regimens to minimize adverse reactions and maximize efficacy
Develop drug-linked diagnostic tests to identify patients who are more likely or less likely to benefit from treatment or who may be at risk of experiencing adverse events
Provide better understanding of mechanisms of disease
Monitor clinical trial participant response to medical interventions
Biomarker research, including research on banked samples, should be recognized as an important public health endeavor for the overall benefit of society, whether by means of advancement of medical science or by development of safer and more effective therapies.[7] Since the value of collected samples may increase over time as scientific discoveries are made, investment in long-term sample repositories is a key component of biomarker research.
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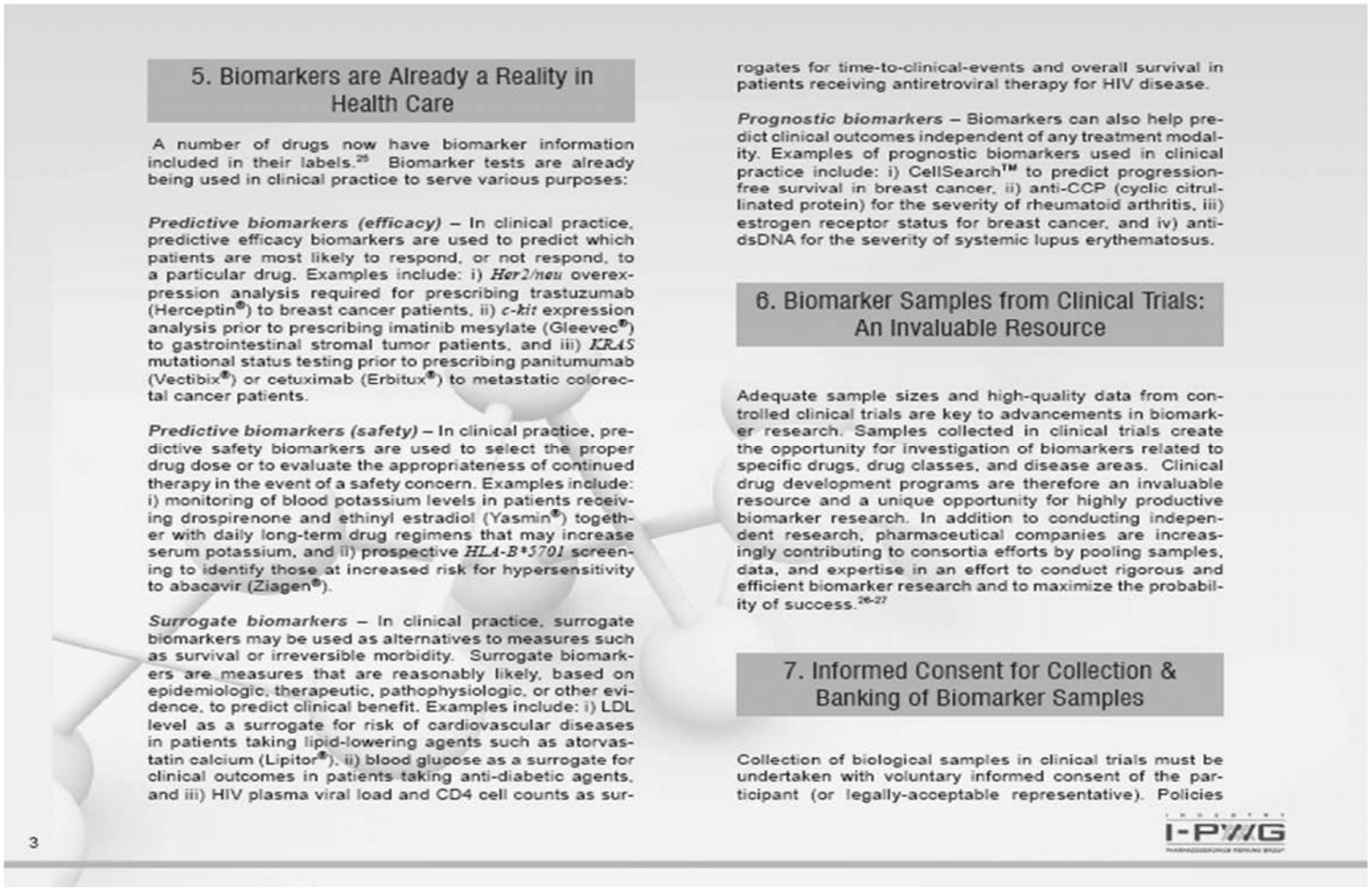

5. Biomarkers are Already a Reality in Health Care

A number of drugs now have biomarker information included in their labels.[25] Biomarker tests are already being used in clinical practice to serve various purposes:

Predictive biomarkers (efficacy) – In clinical practice, predictive efficacy biomarkers are used to predict which patients are most likely to respond, or not respond, to a particular drug. Examples include: i) *Her2/neu* overexpression analysis required for prescribing trastuzumab (Herceptin®) to breast cancer patients, ii) *c-kit* expression analysis prior to prescribing imatinib mesylate (Gleevec®) to gastrointestinal stromal tumor patients, and iii) *KRAS* mutational status testing prior to prescribing panitumumab (Vectibix®) or cetuximab (Erbitux®) to metastatic colorectal cancer patients.

Predictive biomarkers (safety) – In clinical practice, predictive safety biomarkers are used to select the proper drug dose or to evaluate the appropriateness of continued therapy in the event of a safety concern. Examples include: i) monitoring of blood potassium levels in patients receiving drospirenone and ethinyl estradiol (Yasmin®) together with daily long-term drug regimens that may increase serum potassium, and ii) prospective *HLA-B*5701* screening to identify those at increased risk for hypersensitivity to abacavir (Ziagen®).

Surrogate biomarkers – In clinical practice, surrogate biomarkers may be used as alternatives to measures such as survival or irreversible morbidity. Surrogate biomarkers are measures that are reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit. Examples include: i) LDL level as a surrogate for risk of cardiovascular diseases in patients taking lipid-lowering agents such as atorvastatin calcium (Lipitor®), ii) blood glucose as a surrogate for clinical outcomes in patients taking anti-diabetic agents, and iii) HIV plasma viral load and CD4 cell counts as surrogates for time-to-clinical-events and overall survival in patients receiving antiretroviral therapy for HIV disease.

Prognostic biomarkers – Biomarkers can also help predict clinical outcomes independent of any treatment modality. Examples of prognostic biomarkers used in clinical practice include: i) CellSearch™ to predict progression-free survival in breast cancer, ii) anti-CCP (cyclic citrullinated protein) for the severity of rheumatoid arthritis, iii) estrogen receptor status for breast cancer, and iv) anti-dsDNA for the severity of systemic lupus erythematosus.

6. Biomarker Samples from Clinical Trials: An Invaluable Resource

Adequate sample sizes and high-quality data from controlled clinical trials are key to advancements in biomarker research. Samples collected in clinical trials create the opportunity for investigation of biomarkers related to specific drugs, drug classes, and disease areas. Clinical drug development programs are therefore an invaluable resource and a unique opportunity for highly productive biomarker research. In addition to conducting independent research, pharmaceutical companies are increasingly contributing to consortia efforts by pooling samples, data, and expertise in an effort to conduct rigorous and efficient biomarker research and to maximize the probability of success.[26-27]

7. Informed Consent for Collection & Banking of Biomarker Samples

Collection of biological samples in clinical trials must be undertaken with voluntary informed consent of the participant (or legally-acceptable representative). Policies

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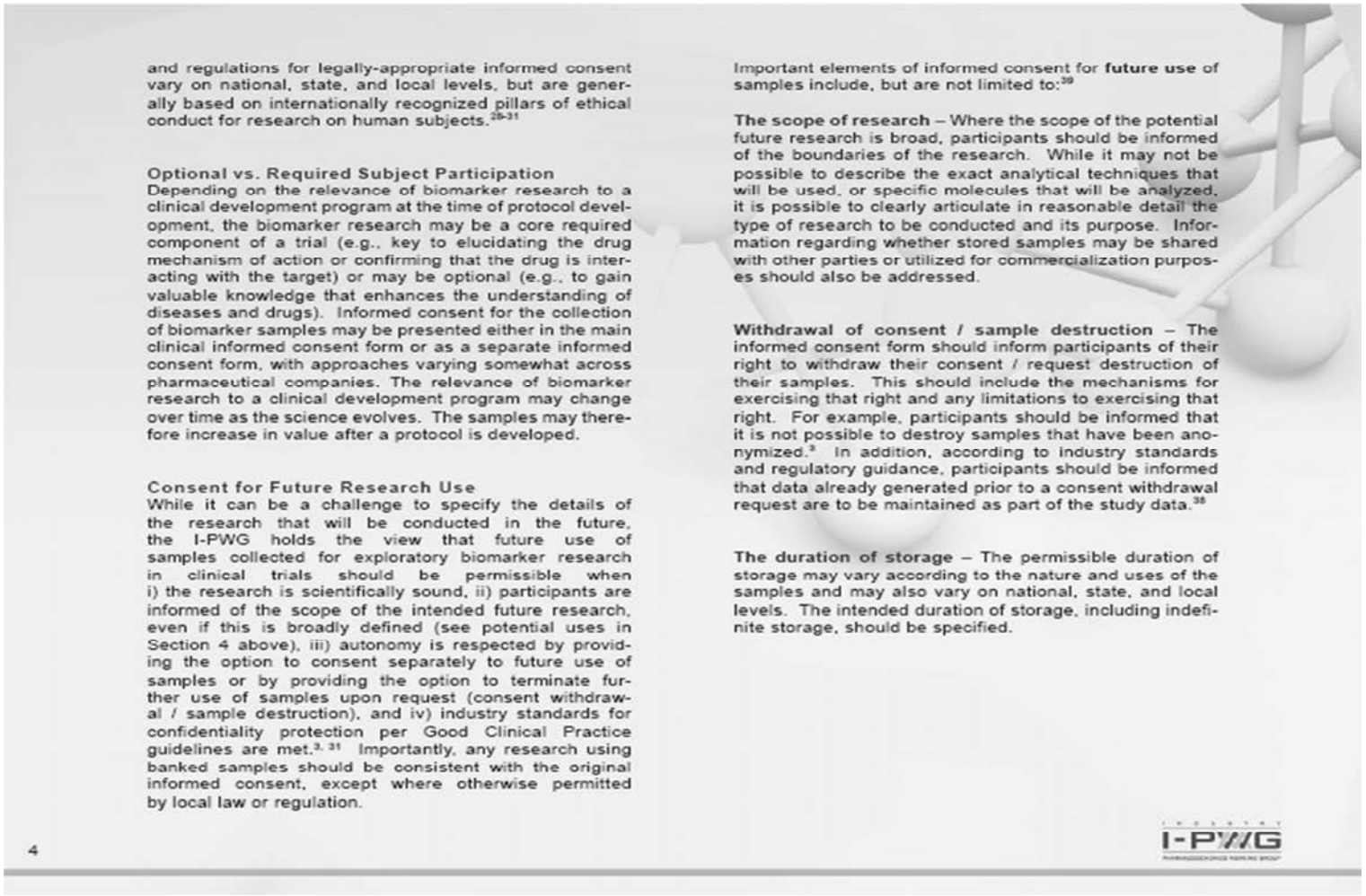

and regulations for legally-appropriate informed consent vary on national, state, and local levels, but are generally based on internationally recognized pillars of ethical conduct for research on human subjects.[26-31]

Optional vs. Required Subject Participation

Depending on the relevance of biomarker research to a clinical development program at the time of protocol development, the biomarker research may be a core required component of a trial (e.g., key to elucidating the drug mechanism of action or confirming that the drug is interacting with the target) or may be optional (e.g., to gain valuable knowledge that enhances the understanding of diseases and drugs). Informed consent for the collection of biomarker samples may be presented either in the main clinical informed consent form or as a separate informed consent form, with approaches varying somewhat across pharmaceutical companies. The relevance of biomarker research to a clinical development program may change over time as the science evolves. The samples may therefore increase in value after a protocol is developed.

Consent for Future Research Use

While it can be a challenge to specify the details of the research that will be conducted in the future, the I-PWG holds the view that future use of samples collected for exploratory biomarker research in clinical trials should be permissible when i) the research is scientifically sound, ii) participants are informed of the scope of the intended future research, even if this is broadly defined (see potential uses in Section 4 above), iii) autonomy is respected by providing the option to consent separately to future use of samples or by providing the option to terminate further use of samples upon request (consent withdrawal / sample destruction), and iv) industry standards for confidentiality protection per Good Clinical Practice guidelines are met.[3, 31] Importantly, any research using banked samples should be consistent with the original informed consent, except where otherwise permitted by local law or regulation.

Important elements of informed consent for **future use** of samples include, but are not limited to:[39]

The scope of research – Where the scope of the potential future research is broad, participants should be informed of the boundaries of the research. While it may not be possible to describe the exact analytical techniques that will be used, or specific molecules that will be analyzed, it is possible to clearly articulate in reasonable detail the type of research to be conducted and its purpose. Information regarding whether stored samples may be shared with other parties or utilized for commercialization purposes should also be addressed.

Withdrawal of consent / sample destruction – The informed consent form should inform participants of their right to withdraw their consent / request destruction of their samples. This should include the mechanisms for exercising that right and any limitations to exercising that right. For example, participants should be informed that it is not possible to destroy samples that have been anonymized.[3] In addition, according to industry standards and regulatory guidance, participants should be informed that data already generated prior to a consent withdrawal request are to be maintained as part of the study data.[38]

The duration of storage – The permissible duration of storage may vary according to the nature and uses of the samples and may also vary on national, state, and local levels. The intended duration of storage, including indefinite storage, should be specified.

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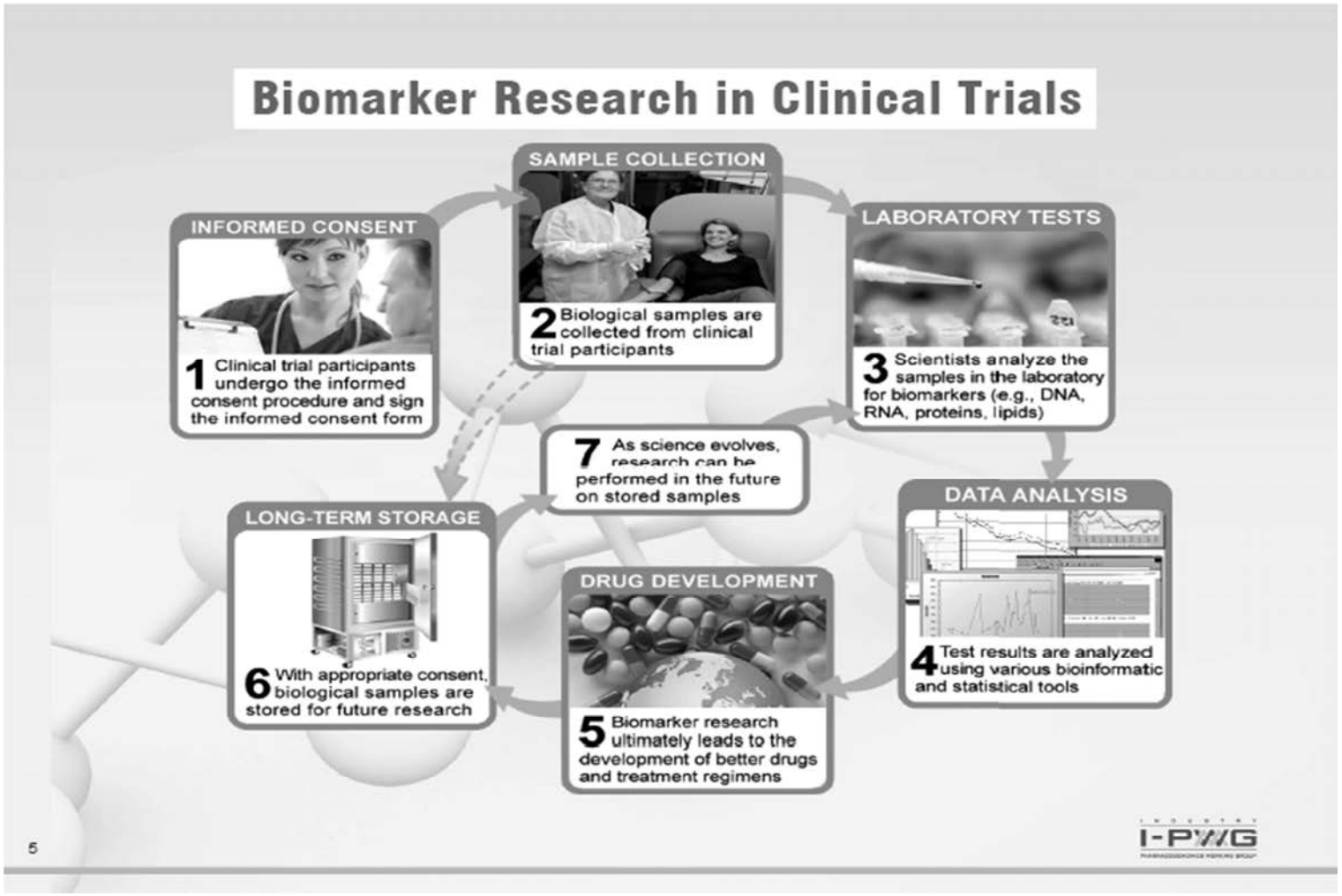
Biomarker Research in Clinical Trials
SAMPLE COLLECTION
2 Biological samples are collected from clinical trial participants
INFORMED CONSENT
1 Clinical trial participants undergo the informed consent procedure and sign the informed consent form
LABORATORY TESTS
3 Scientists analyze the samples in the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

Collection of biological samples for biomarker research is straightforward in most jurisdictions. Some countries have specific laws and regulations regarding collection, labeling, storage, export, and/or use of exploratory samples. In addition, some regulations distinguish between DNA and non-DNA samples or between samples used for diagnostic purposes and samples collected for scientific research. Processes for the collection, labeling, storage, export, and/or use of biomarker samples should always adhere to the laws and regulations of the country/region in which those samples are collected.

9. Return of Research Results to Study Participants

Policies for the return of biomarker research results to study participants who request them vary among pharmaceutical companies. There are many considerations that pharmaceutical companies weigh when determining their policy regarding the return of biomarker research results to study participants. These include:

i) the conditions under which biomarker research results were generated (i.e., exploratory research laboratory versus accredited diagnostic laboratory)

ii) whether the results will have an impact on the medical care of the participant or on a related person, if applicable

iii) whether genetic counseling is recommended (for genetic results)

iv) the ability to accurately link the result to the individual from whom the sample was collected

v) international, national, and local guidelines, policies, legislation, and regulations regarding participants' rights to access data generated on them

Renegar *et al*. 2006 and Article 29 Data Protection Working Party (an advisory committee to the European Commission on the European Data Protection Directive) have addressed these considerations in detail in relation to pharmacogenomic research data and provided a list of documents addressing the general issue of return of research results.[34-35]

10. Benefits and Risks Associated with Biomarker Research

Benefits
While it may not always directly benefit the study participant who is providing the samples, biomarker research can improve overall understanding of disease and treatment of future patients receiving therapies developed from such research. Patients are now benefiting from retrospective biomarker research conducted on samples collected from clinical trials and stored for exploratory research. One example is the recent label update to the EGFR antibody drugs cetuximab (Erbitux®) and panitumumab (Vectibix®) which highlights the value of *KRAS* status as a predictive biomarker for treatment of metastatic colorectal cancer with this class of drug.

The humanitarian benefit of human research is recognized by the Nuremberg Code.[28,33] Provided that the degree of risk does not exceed that determined by the humanitarian importance of the problem to be solved, research participants should not be denied the right to contribute to the greater common good.[28,32]

Risks
Risks associated with biomarker research are primarily related to the physical aspects of obtaining the sample and to patient privacy concerns.

Physical risks associated with biomarker sample collection in clinical trials can be characterized in two ways: i) negligible additional risk when the biomarker sample is collected as part of a procedure conducted to support

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other core trial objectives, and ii) some added risk where the sampling procedure would otherwise have not been performed as a core component of a trial. Risks are also determined by the invasiveness of the sample collection procedure.

Privacy risks are generally those associated with the inappropriate disclosure and misuse of data. Pharmaceutical companies have policies and procedures for confidentiality protection to minimize this risk for all data collected and generated in clinical trials. These may vary across companies, but are based on industry standards of confidentiality and privacy protection highlighted in the following section. Importantly, privacy risks inherent to biomarker data are no greater than other data collected in a clinical trial.

11. Privacy, Confidentiality, and Patient Rights

Maintaining the privacy of study participants and the confidentiality of information relating to them is of paramount concern to industry researchers, regulators, and patients. Good Clinical Practice (GCP), the standard adhered to in pharmaceutical clinical research, is a standard that

"...provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected",

where confidentiality is defined as, *"The prevention of disclosure, to other than authorized individuals, of a sponsor's proprietary information or of a subject's identity."*

This standard dictates that *"the confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with applicable regulatory requirements."* [31]

Exploratory biomarker research in pharmaceutical development is commonly conducted in research laboratories that are not accredited to perform diagnostic tests used for healthcare decision-making. Therefore, results from exploratory biomarker research usually are not appropriate for use in making decisions about a trial participant's health. In addition, exploratory research data should not be included as part of a participant's medical record accessible for use by insurance companies. Legislation and policies to protect individuals against discrimination based on genetic information continually evolve based on social, ethical, and legal considerations. Examples of such legislation include the Human Tissue Act 2004 (UK) and the Genetic Information Nondiscrimination Act (GINA) 2008 (USA).[36-37]

12.Where to Get More Information?

Educational resources related to biomarker and pharmacogenomic research that caters to health care professionals, IRBs/IECs, scientists, and patients are continually being created and are publicly available. Links to many of these resources are available through the I-PWG website: www.i-pwg.org.

13. What is I-PWG?

The Industry Pharmacogenomics Working Group (I-PWG) (formerly the Pharmacogenetics Working Group) is a voluntary association of pharmaceutical companies engaged in pharmacogenomic research. The Group's activities focus on non-competitive educational, informational, ethical, legal, and regulatory topics. The Group provides information and expert opinions on these topics and sponsors educational/informational programs to promote better understanding of pharmacogenomic and other biomarker research for key stakeholders. The I-PWG interacts with regulatory author-

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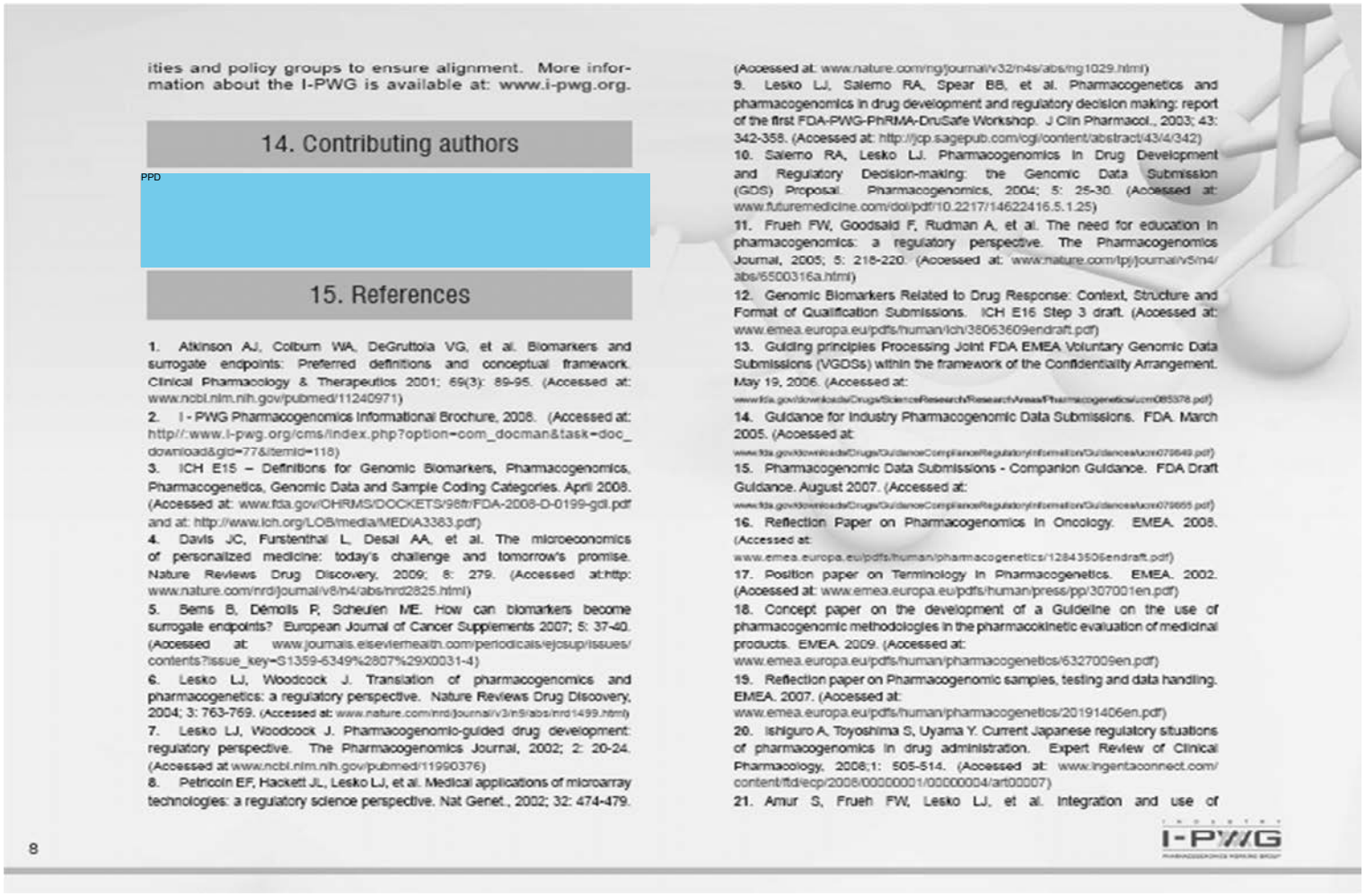

ities and policy groups to ensure alignment. More information about the I-PWG is available at: www.i-pwg.org.

14. Contributing authors

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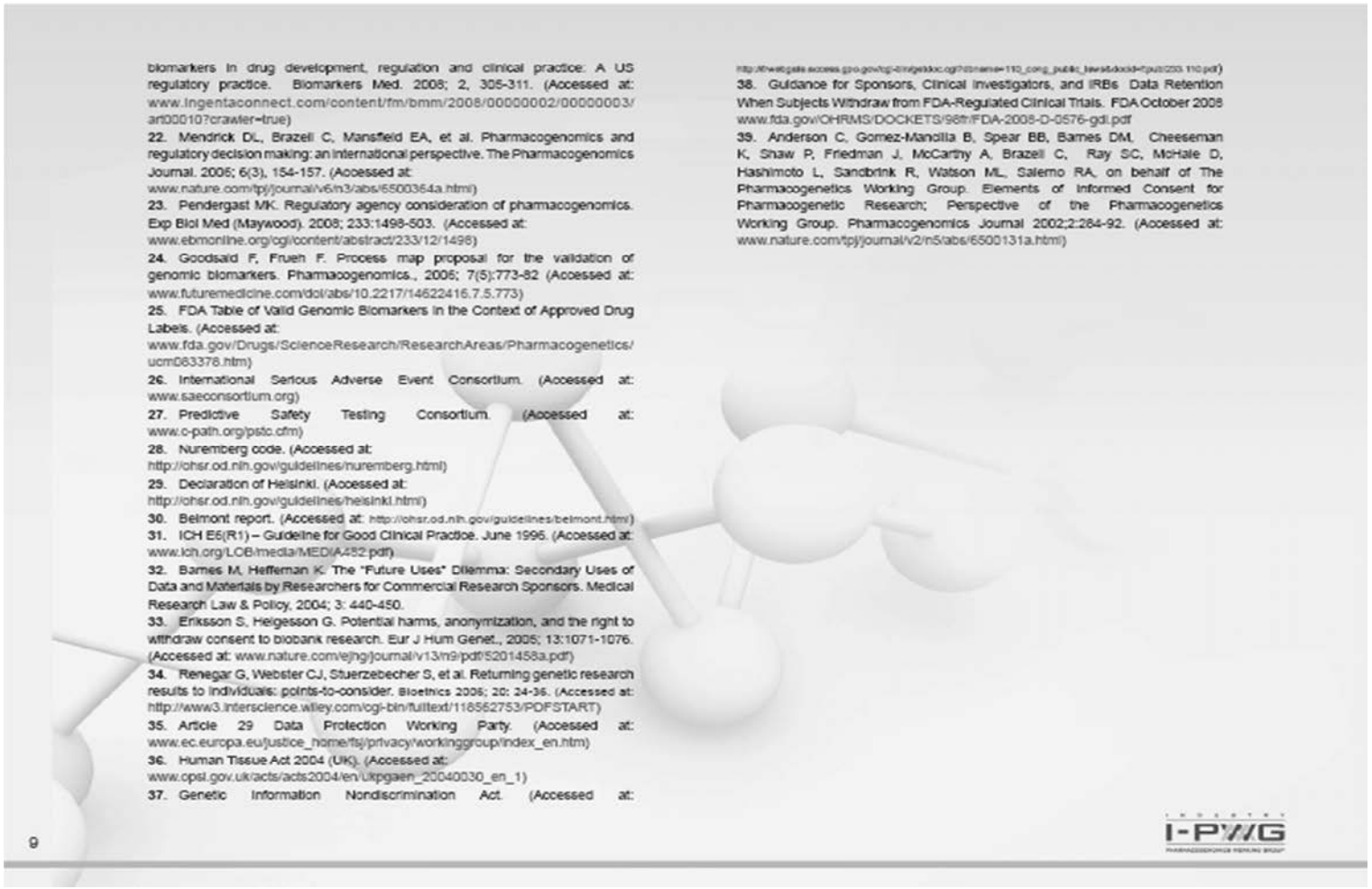

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12.4 List of Abbreviations

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
BICR	Blinded independent central review
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
eDMC	external Data Monitoring Committee
DOR	Duration of response
EBUS	Endobronchial Ultrasound
ECI	Events of clinical interest
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EGFR	epidermal growth factor receptor
EMA	European Medicines Agency
ERC	Ethics review committee
FA	Final analysis
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
HR	Hazard ratio
IA1	Interim analysis (first)
IA2	Interim analysis (second)
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Conference on Harmonization
IHC	Immunohistochemistry
irRC	immune-related response criteria
irRECIST	Immune-related Response Evaluation Criteria in Solid Tumors
INR	International normalized ratio
irAEs	Immune-related adverse events

Abbreviation/Term	Definition
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.
MTD	Maximum tolerated dose
NA or N/A	Not Applicable
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NSCLC	non-small cell lung cancer (NSCLC)
ORR	Objective response rate
OS	Overall survival
OTC	Over-the-counter
PD	Progressive disease
PD-L1	Programmed cell death ligand-1
PET	Positron emission tomography
PFS	Progression free survival
PFS2	next line of therapy PFS2
PGt	Pharmacogenetic
PK	Pharmacokinetic
PK-PD	Pharmacokinetic-Pharmacodynamic
PRO	patient reported outcome
PR	Partial response
PT	Prothrombin time
Q-TWiST	Quality-adjusted Time without Symptoms or Toxicity
RCC	renal cell carcinoma
RNA	Ribonucleic acid
RECIST	Response Evaluation Criteria in Solid Tumors RECIST 1.1
RR	Response rate
Q3W	Every 3 weeks
SAE	Serious adverse events
SAP	Statistical Analysis Plan
SD	Stable disease
SFU	Survival follow-up
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SOC	Standard of Care
T1DM	Type 1 Diabetes Mellitus
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

12.5 Calculated Creatinine Clearance

Original, Weight-Based Cockcroft and Gault Formula for Calculated Creatinine Clearance for Men

For serum creatinine concentration in mg/dL:

$$\text{CrCl (mL/min)} = \frac{(140 - \text{age}^a) \times (\text{wt}^b) \times 1.0}{72 \times \text{serum creatinine (mg/dL)}}$$

For serum creatinine concentration in μmol/L:

$$\text{CrCl (mL/min)} = \frac{(140 - \text{age}^a) \times (\text{wt}^b) \times 1.0}{0.81 \times \text{serum creatinine (μmol/L)}}$$

[a] Age in years.

[b] Weight (wt) in kilograms.

Source: Cockcroft and Gault 1976.

Original, Weight-Based Cockcroft and Gault Formula for Calculated Creatinine Clearance for Women

For serum creatinine concentration in mg/dL:

$$\text{CrCl (mL/min)} = \frac{(140 - \text{age}^a) \times (\text{wt}^b) \times 0.85}{72 \times \text{serum creatinine (mg/dL)}}$$

For serum creatinine concentration in μmol/L:

$$\text{CrCl (mL/min)} = \frac{(140 - \text{age}^a) \times (\text{wt}^b) \times 0.85}{0.81 \times \text{serum creatinine (μmol/L)}}$$

[a] Age in years.

[b] Weight (wt) in kilograms.

Source: Cockcroft and Gault 1976.

Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron. 1976;16:31–41

12.6 MASCC corticosteroid dosing guidelines (2013 guidelines or more current guidelines, if available)

Recommended Corticosteroid* (dexamethasone) Dosing

DEXAMETHASONE		Dose and Schedule
High Risk	- Acute Emesis	20 mg once (12 mg when used with aprepitant or fosaprepitant)**
	- Delayed Emesis	8 mg bid for 3 - 4 days (8 mg once daily when used with aprepitant or fosaprepitant)
Moderate Risk	- Acute Emesis	8 mg once
	- Delayed Emesis	8 mg daily for 2 - 3 days (many panelists give the dose as 4 mg bid)
Low Risk	- Acute Emesis	4 - 8 mg once

* While corticosteroids other than dexamethasone are effective antiemetics, the dose and schedule of dexamethasone coupled with its wide availability in various dose forms established it as the guideline agent of choice

** The 12 mg dose of dexamethasone is the only one tested with aprepitant in large randomized trials

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12.7 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)

12.8 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, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.* The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.

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	