Official Protocol Title:	A Randomized, Double-Blind, Phase III Study of Carboplatin-Paclitaxel/Nab-Paclitaxel Chemotherapy with or without Pembrolizumab (MK-3475) in First Line Metastatic Squamous Non-small Cell Lung Cancer Subjects (KEYNOTE-407)
NCT number:	NCT02775435
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TITLE:

A Randomized, Double-Blind, Phase III Study of Carboplatin-Paclitaxel/Nab-Paclitaxel Chemotherapy with or without Pembrolizumab (MK-3475) in First Line Metastatic Squamous Non-small Cell Lung Cancer Subjects (KEYNOTE-407)

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DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Amendment 08	25-JUL-2022	Global amendment, including China: Added language to allow participants in the crossover phase of the study to be eligible for second-course treatment with pembrolizumab and to allow participants in first-course follow-up to be eligible for second-course treatment for longer than 2 years.
Amendment 07	04-JAN-2022	Global amendment, including China: Added language regarding the enrollment of subjects in a pembrolizumab extension study upon study completion.
Amendment 06	30-OCT-2019	China amendment: Interim results were positive and therefore subjects are to be given the option of discontinuing placebo treatment.
Amendment 05	28-JUN-2018	Global amendment: Interim results were positive and therefore subjects are to be given the option of discontinuing placebo treatment.
Amendment 04	20-NOV-2017	China amendment: The statistical design was updated to optimize the study for the identification of long-term treatment effect in OS and PFS.
Amendment 03	13-NOV-2017	The statistical design was updated to optimize the study for the identification of long-term treatment effect in OS and PFS.
Amendment 02	26-OCT-2017	The statistical design was updated to optimize the study for the identification of long-term treatment effect in OS and PFS.
Amendment 01	27-JUL-2017	China amendment: To extend the enrollment period beyond the global study to achieve required number of Chinese subjects and events to investigate efficacy and safety in Chinese NSCLC subjects.
Original Protocol	24-MAR-2016	Not applicable.

SUMMARY OF CHANGES

PRIMARY REASON(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
1.1 7.1.5.5	Trial Summary Second Course Phase	Language added to allow participants in the crossover phase of the study to receive second course treatment if eligible.	To expand the treatment opportunities of eligible study participants in the crossover phase.
7.1.5.3	Post-Trial	Specification that study participants will be followed for up to 2 years replaced with specification that study participants will be followed for disease status.	To allow study participants in first-course follow-up to be eligible for second-course treatment for longer than 2 years.

ADDITIONAL CHANGE(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
Title Page 12.1	Title Page Code of Conduct for Clinical Trials	Sponsor entity name and address changed.	Merck Sharp & Dohme Corp. underwent an entity name and address change to Merck Sharp & Dohme LLC, Rahway, NJ, USA. This conversion resulted only in an entity name change and update to the address.
5.1	Entry Criteria	Language related to the collection of demographic data added.	To clarify the collection, use, and confidentiality of demographic data provided by study participants.
5.1.2 5.7.2	Subject Inclusion Criteria Contraception	Contraception requirements clarified.	To specify the requirements during and after treatment with chemotherapy vs. pembrolizumab.
5.2	Trial Treatments	Study intervention table updated.	To align with the EU CTR.
7.1.5.5	Second Course Phase	Eligibility for second course phase updated from 17 cycles to 35 treatments.	To align with the program standard.
Throughout as applicable	Throughout as applicable	Typographical corrections and minor administrative edits made.	To correct typographical errors and clarify intended meaning.

1.0 TRIAL SUMMARY

Abbreviated Title	Phase III study of carboplatin and paclitaxel or nano particle albumin-bound paclitaxel (nab-paclitaxel) with or without pembrolizumab in first line metastatic squamous NSCLC.
Sponsor Product Identifiers	MK-3475 pembrolizumab
Trial Phase	Phase III
Clinical Indication	Treatment of metastatic squamous non-small cell lung cancer
Trial Type	Interventional
Type of control	Placebo-control
Route of administration	Intravenous
Trial Blinding	Double-blind
(Select Groups)	There are 2 treatment arms: • Pembrolizumab plus carboplatin and paclitaxel or nab-paclitaxel • Saline placebo plus carboplatin and paclitaxel or nab-paclitaxel
Number of trial subjects	Approximately 560 subjects will be enrolled in the global trial.
Estimated duration of trial	The Sponsor estimates that the trial will require approximately 4 years from the time the first subject (or their legally acceptable representative) provides documented informed consent until the last subject's last study-related contact.
Duration of Participation	Each subject will participate in the study from the time the subject (or their legally acceptable representative) provides documented informed consent 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. All subjects will receive up to a maximum of 4 cycles of carboplatin, paclitaxel or nab-paclitaxel and pembrolizumab or saline placebo. Treatment with pembrolizumab or saline placebo will continue until total of 35 treatment administrations of pembrolizumab or saline placebo 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. Because of positive interim results, this study is being unblinded. Subjects assigned to the placebo arm may discontinue treatment with normal saline placebo and have the option of receiving pembrolizumab. Subjects on pembrolizumab arm will continue until total of 35 treatment administration. Subjects who experience documented disease progression verified by central imaging vendor will have treatment assignment unblinded and be able to continue on open-label pembrolizumab monotherapy in the Crossover Phase. The details are outlined in Section 7.1.5.6. Subjects who attain a complete response verified by central imaging vendor and have been on pembrolizumab/ therapy for ≥ 8 cycles, may consider stopping trial treatment. These subjects, as well as those subjects assigned to the pembrolizumab arm or who crossover 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 in the Second Course Phase after they have experienced radiographic disease progression at the discretion of the investigator according to the criteria in Section 7.1.5.5. 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). 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. All subjects will be followed for overall survival until death, lost to follow up or withdrawal of consent.

Randomization Ratio	Randomized 1:1 to either receive pembrolizumab combined with carboplatin and investigators choice of paclitaxel or nab-paclitaxel, or saline placebo combined with carboplatin and investigators choice of paclitaxel or nab-paclitaxel.

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, placebo-controlled with active treatment, parallel-group, multi-site, double-blind trial of IV pembrolizumab (also known as MK-3475) combined with carboplatin-paclitaxel/nab-paclitaxel chemotherapy versus saline placebo combined with carboplatin-paclitaxel/nab-paclitaxel chemotherapy in subjects with metastatic squamous NSCLC who have not previously received systemic therapy for metastatic disease (1L).

Approximately 560 eligible subjects will be enrolled into this trial to examine the efficacy of pembrolizumab combined with chemotherapy compared to chemotherapy alone. Subjects will be randomized 1:1 as indicated below:

- Arm 1: Pembrolizumab 200 mg (Day 1) + carboplatin AUC 6 (D1) + paclitaxel 200 mg/m^2 (D1) OR nab-paclitaxel 100 mg/m^2 (D1, D8, D15) Q3W for 4 cycles followed by pembrolizumab 200 mg (D1) Q3W until progression.
- Arm 2: Saline placebo + carboplatin AUC 6 (D1) + paclitaxel 200 mg/m^2 (D1) OR nab-paclitaxel 100mg/m^2 (D1, D8, D15) Q3W for 4 cycles followed by saline placebo (D1) Q3W until progression.

Because of positive interim results, this study was unblinded so that subjects assigned to the placebo arm (Arm 2) may discontinue treatment with normal saline placebo and have the option of receiving pembrolizumab if there is documented progressive disease by central radiological review.

Subjects will receive up to 4 cycles of pembrolizumab or saline placebo with chemotherapy followed by pembrolizumab or saline placebo Q3W as maintenance therapy. Please refer to Figure 1 for detailed study design.

Subjects will be stratified by paclitaxel vs. nab-paclitaxel, PD-L1 status (TPS ≥1% vs. <1%; PD-L1 non-evaluable subjects will be included with the TPS <1% group), and geographic region of the enrolling site (East Asia vs. non-East Asia) prior to randomization.

After randomization, subjects will be evaluated with radiographic imaging to assess response to treatment with the schedule outlined in Section 7.1.2.6.2; treatment-based decisions should be made using irRECIST (details are provided in Section 7.1.2.6.6 and the Merck TIP Sheet). All imaging obtained on study will be submitted to a blinded independent central imaging vendor who will assess the images using RECIST 1.1 for determination of ORR and PFS by RECIST 1.1. AE monitoring will be ongoing throughout the trial and graded in severity according to the guidelines outlined in the NCI CTCAE, version 4.0.

Treatment with pembrolizumab or saline placebo will continue until a total of 35 treatments have been administered, subject withdrawal, or other discontinuation criteria is met as outlined in Section 5.8.

Treatment-based decisions will be made by local radiological review based on irRECIST and the disease progression will be verified by central radiological review. At the time of documented progression verified by a blinded independent central imaging vendor review per RECIST 1.1, subjects will have treatment assignment unblinded and be able to continue therapy in the Crossover Phase as indicated below:

1. Subjects who had received saline placebo will be able to receive open-label pembrolizumab monotherapy for a total of 35 treatments.
2. Subjects who had received pembrolizumab, 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.

The details regarding Crossover Phase is outlined in Section 7.1.5.6.

Subjects who attain a CR verified by central radiological review may consider stopping trial treatment. These subjects, as well as those subjects assigned to the pembrolizumab arm or who crossover 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 open-label pembrolizumab monotherapy after they have experienced radiographic disease progression at the discretion of the investigator according to defined criteria in Section 7.1.5.5. This re-treatment will be the Second Course Phase. Response or progression in the Second Course Phase will not count toward the ORR and PFS endpoints in this trial.

After the end of treatment, each subject will be followed for a minimum of 30 days for AE monitoring. 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.

This trial has dual primary endpoints: 1) PFS per RECIST 1.1 by a blinded independent central imaging vendor review and 2) OS. The trial will be considered positive if the hypothesis test for either one of these primary endpoints is successful. Other secondary endpoints include ORR and DOR per RECIST 1.1 by a blinded independent central imaging vendor review, and safety as assessed by a variety of parameters of AEs. Exploratory analyses include PFS by investigator-assessed irRECIST, ORR by investigator-assessed irRECIST, PFS, OS and ORR in different PD-L1 subgroups and PFS, OS and ORR in subgroups based on the choice of taxane therapy. Drug-drug interaction studies and quality of life assessments are further exploratory endpoints.

Participation in this trial will be dependent upon supplying tumor tissue for PD-L1 testing. The details of tumor tissue requirements are outlined in Section 7.1.2.7. 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.

There are 4 analyses planned for this study: 3 IAs and the final analysis. Results from the 3 IAs will be reviewed by an external data monitoring committee. The details regarding the timing and purpose of each analysis are provided in Section 8.7.

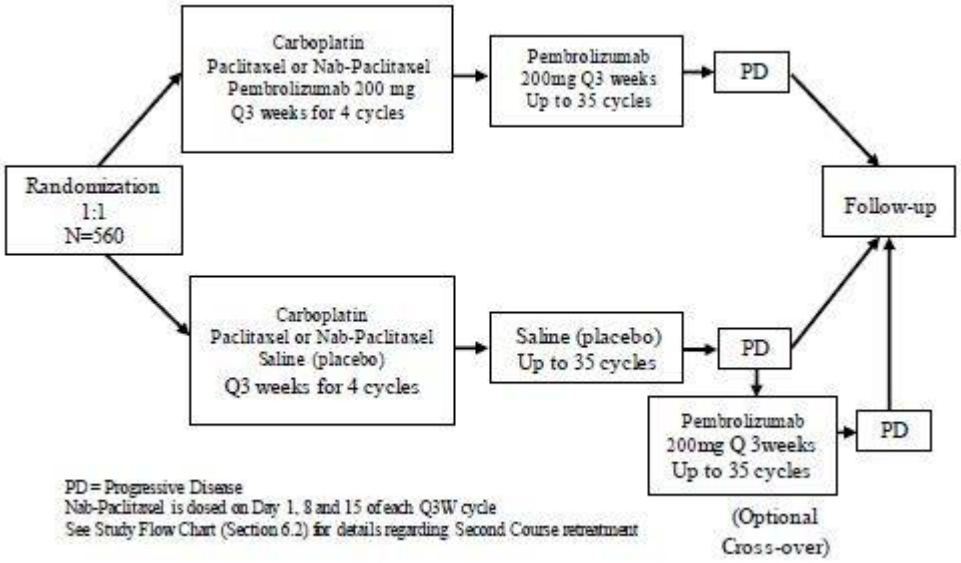
See Appendix 12.7 for country-specific information.

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)

3.1 Primary Objective(s) & Hypothesis(es)

In 1L subjects with metastatic squamous NSCLC receiving investigator's choice of SOC chemotherapy (ie, carboplatin and a taxane):

1. Objective: Evaluate progression free survival (PFS) per RECIST 1.1 as assessed by a central imaging vendor in subjects treated with pembrolizumab compared to placebo.

   Hypothesis: Pembrolizumab prolongs PFS by RECIST 1.1 as assessed by a central imaging vendor compared to placebo.

2. Objective: Evaluate overall survival (OS) in subjects treated with pembrolizumab compared to placebo.

   Hypothesis: Pembrolizumab prolongs OS compared to placebo.

3.2 Secondary Objective(s) & Hypothesis(es)

In 1L subjects with metastatic squamous NSCLC receiving investigator's choice of SOC chemotherapy (ie, carboplatin and a taxane):

1. Objective: Evaluate the objective response rate (ORR) and duration of response (DOR) per RECIST 1.1 as assessed by a central imaging vendor in subjects treated with pembrolizumab compared to placebo.

   Hypothesis: Pembrolizumab improves ORR per RECIST 1.1 as assessed by a central imaging vendor compared to placebo.

2. Objective: Evaluate the safety and tolerability profile of pembrolizumab.

3.3 Exploratory Objectives

In 1L subjects with metastatic squamous NSCLC receiving investigator's choice of SOC of chemotherapy (ie, carboplatin and a taxane):

1) Objective: Evaluate pembrolizumab compared to placebo with respect to:
   a. PFS per RECIST 1.1 as assessed by investigator review in the next line of therapy (PFS2).
   b. PFS per irRECIST as assessed by site investigator.
   c. ORR and DOR per irRECIST as assessed by site investigator.
   d. PFS and ORR per RECIST 1.1 as assessed by central imaging vendor and OS by PD-L1 status (≥1% vs. <1%) and by taxane (investigators choice of paclitaxel or nab-paclitaxel).
2) To investigate the relationship between pembrolizumab treatment and biomarkers predicting response (eg, PD-L2, genetic variation, serum PD-L1) utilizing newly obtained or archival FFPE tumor tissue and blood, including serum and plasma.

3) To evaluate changes in health-related quality-of-life assessments from baseline in the overall study population and by PD-L1 expression level using the EORTC QLQ-C30 and EORTC QLQ-LC13.
4) To characterize utilities in subjects treated with pembrolizumab and chemotherapy compared to saline placebo and chemotherapy using the EuroQoL(EQ)-5D.
5) To characterize the pharmacokinetic characteristics of carboplatin, paclitaxel/nab-paclitaxel treatment, and pembrolizumab.
6) To identify molecular (genomic, metabolic and/or proteomic) biomarkers that may be indicative of clinical response/resistance, safety, pharmacodynamic activity, and/or the mechanism of action of pembrolizumab and other treatments.

4.0 BACKGROUND & RATIONALE

4.1 Background

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

4.1.1 Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades [1]. Accumulating evidence shows a correlation between 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 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, Tregs 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. 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 [18], pancreatic carcinoma [19], hepatocellular carcinoma [20], and ovarian carcinoma. [21] Furthermore, PD-1 has been suggested to regulate tumor-specific T-cell expansion in subjects with melanoma [22].

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 monotherapy in models of squamous cell carcinoma, pancreatic carcinoma, melanoma, and colorectal carcinoma. Blockade of the PD-1 pathway effectively promoted CD8+ T-cell infiltration into the tumor and the presence of IFN-gamma, granzyme B and perforin, indicating that the mechanism of action involved local infiltration and activation of effector T-cell function in vivo [21] [23] [24] [25] [26] [27]. 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).

Pembrolizumab is a highly selective humanized mAb that binds to the PD-1 receptor and directly blocks the interaction between PD-1 and its ligands, thereby enhancing tumor regression and ultimately immune rejection (see the IB). Pembrolizumab is being investigated in various oncology indications including melanoma, NSCLC, RCC, breast cancer, multiple myeloma, microsatellite unstable tumors, and head and neck cancer. Pembrolizumab [Keytruda (US)], is approved for treatment of melanoma in several countries; in the US it is indicated for the treatment of advanced, unresectable or metastatic malignant melanoma in subjects with disease progression after prior treatment with ipilimumab and, for BRAF V600 mutation-positive patients, a BRAF inhibitor, while in the EU it is approved for the treatment of advanced (unresectable or metastatic) melanoma in adults. Pembrolizumab has also been granted approval in the US for the treatment of subjects with metastatic NSCLC whose tumors express PD-L1 as determined by an FDA-approved test and who have disease progression on or after platinum-containing chemotherapy.

An open-label Phase 1 trial (KEYNOTE-001) is being conducted to evaluate the safety and clinical activity of single-agent pembrolizumab. The dose escalation portion of this trial evaluated 3 dose levels, 1 mg/kg, 3 mg/kg, and 10 mg/kg, administered every 2 weeks, in subjects with advanced solid tumors. All 3 dose levels were well tolerated and no DLTs were observed. Based on PK data showing a half-life of 21 days, the dosing frequency in the expansion cohort has been changed to Q3W [28].

In the same open-label multi-cohort Phase 1 trial (KEYNOTE-001), a total of 550 NSCLC subjects were treated with at least 1 dose of pembrolizumab in several dose expansion

cohorts. The initial data from 495 NSCLC subjects were published and reported. The ORR was 19.4% (18.0% in the 394 previously-treated subjects and 24.8% in the 101 previously-untreated subjects). The response rate 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 (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 [29].

Pembrolizumab has been generally well tolerated. The most common treatment-related AEs were fatigue (19.4%), pruritus (10.7%), and decreased appetite (10.5%). Adverse events of Grade 3 or higher were reported in 47 of 495 subjects (9.5%). The only treatment-related AEs of an inflammatory or immune-mediated nature that occurred in more than 2% of patients were infusion-related reactions (in 15 patients [3.0%]), hypothyroidism (in 34 patients [6.9%]), and pneumonitis (in 18 patients [3.6%]). One infusion reaction led to treatment discontinuation. All the patients with hypothyroidism were successfully treated with medical therapy [28].

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). Pembrolizumab monotherapy compared to placebo is also being evaluated in patients with early-stage NSCLC after resection and completion of standard adjuvant therapy (KEYNOTE-091).

Several ongoing trials are exploring different combinations of pembrolizumab with chemotherapy, targeted therapy and other immunotherapy. An ongoing Phase 1b/2 study (KEYNOTE-021) explored different chemotherapy combinations with pembrolizumab; preliminary data presented at ASCO 2015 suggest a manageable toxicity profile. In Cohort A of KEYNOTE-021, 25 subjects with NSCLC were treated with 4 cycles of carboplatin, paclitaxel, and pembrolizumab followed by maintenance pembrolizumab Q3W. There were no DLTs or treatment-related deaths reported in Cohort A. Approximately 96% of patients experienced ≥1 treatment-related AE of any grade with the most common treatment-related AEs being alopecia, fatigue, and nausea. Overall, the toxicity profile from the combination was compatible with what would be expected with chemotherapy alone. The preliminary data using investigator-assessed response rate based on RECIST 1.1 was 25% in all comers and the responses were durable. In the exploratory analysis of 9 subjects with squamous cell NSCLC, the ORR was 55.6 % (95% CI: 21.2 to 86.3) with a disease control rate of 100%; median PFS and DOR were not reached. Responses were seen in both PD-L1 positive and PD-L1 negative patients. An ongoing Phase 1b/2 study (KEYNOTE-026) is exploring the combination of pembrolizumab with carboplatin and nab-paclitaxel. Preliminary safety

results from this trial show that the combination of carboplatin/nab-paclitaxel and pembrolizumab was safe and tolerable and the most common AEs were hematologic toxicities. Two of the initial 12 subjects treated in the Phase 1 portion of the study had a DLT: Grade 4 hyperglycemia and Grade 3 febrile neutropenia. The Phase 2 portion of the study is ongoing.

4.1.4 Information on Other Trial-Related Therapy

Platinum doublet chemotherapy is the SOC for the treatment of patients with good performance status (ECOG 0 or 1), advanced or metastatic, previously untreated squamous NSCLC. Treatments include cisplatin or carboplatin in combination with paclitaxel, gemcitabine, or docetaxel [30]. Multiple Phase 3 studies have demonstrated similar efficacy for most platinum doublets in NSCLC patients, Study ECOG 1594 being the most cited [31].

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 to 1.15; p=0.10). These data support the interchangeable use of carboplatin or cisplatin in combination with SOC antineoplastic agents [32].

A randomized Phase 3 trial compared the efficacy and safety of nab-paclitaxel plus carboplatin with sb-paclitaxel plus carboplatin in advanced NSCLC. A total of 1,052 untreated subjects with Stage IIIB to IV NSCLC were randomly assigned 1:1 to receive 100 mg/m^2 nab-paclitaxel weekly and carboplatin at AUC of 6 Q3W (nab-paclitaxel) or 200 mg/m^2 sb-paclitaxel plus carboplatin AUC 6 Q3W (sb-paclitaxel). The primary end point was ORR. The ORR in the nab-paclitaxel and sb-paclitaxel arms were 33% vs. 25% respectively (response rate ratio, 1.313; 95% CI: 1.082 to 1.593). In subjects with squamous histology, the ORR was 41% vs. 24% (response rate ratio, 1.680; 95% CI: 1.271 to 2.221). However, there were no significant differences in PFS (median, 6.3 vs. 5.8 months; HR, 0.902; 95% CI: 0.767 to 1.060; p=0.214) and OS (median, 12.1 vs. 11.2 months; HR, 0.922; 95% CI: 0.797 to 1.066; p=0.271) in the nab-paclitaxel arm versus the sb-paclitaxel arm, respectively. Significantly less Grade 3 neuropathy, neutropenia, arthralgia, and myalgia occurred in the nab-paclitaxel arm, and less thrombocytopenia and anemia occurred in the sb-paclitaxel arm [33].

Recently, an open-label, randomized, active controlled Phase 2 trial evaluated nab-paclitaxel and carboplatin compared with gemcitabine and carboplatin as first-line therapy in locally advanced or metastatic squamous NSCLC. A total of 120 untreated advanced squamous NSCLC subjects were randomized at a 1:1 ratio to receive nab-paclitaxel (135 mg/m^2, D1, D8, Q3W) plus carboplatin (AUC 5, D1, Q3W) or gemcitabine (1,250 mg/m^2, D1, D8, Q3W) and carboplatin (AUC 5, D1, Q3W). The primary endpoint was ORR and the secondary endpoints were PFS, OS, safety, and biomarkers associated with nab-paclitaxel. The preliminary results from this trial were presented at ASCO 2014. There were 110 cases evaluable for ORR (nab-paclitaxel, 54; gemcitabine, 56), 119 evaluable for OS (nab-paclitaxel, 57; gemcitabine, 62) and 124 evaluable for safety (nab-paclitaxel, 59;

gemcitabine, 65), respectively. ORR was 46.3% (25/54) for the nab-paclitaxel arm and 30.4% (17/56) for the gemcitabine arm respectively, p=0.085. The median PFS was 5.7 vs. 4.8 months (HR, 0.907; 95% CI: 0.588 to 1.399; p=0.657) in the nab-paclitaxel arm vs. the gemcitabine arm. Overall survival was not mature [34].

Recently, a large, randomized trial evaluated necitumumab, a second-generation, mAb against EGFR in subjects with previously untreated Stage IV squamous NSCLC. In this study, 1093 subjects were randomly assigned to receive necitumumab plus gemcitabine and cisplatin (n=545) or gemcitabine and cisplatin (n=548). The ORR was 31% in the necitumumab plus chemotherapy and 29% in the chemotherapy alone arms, respectively. The median PFS was 5.7 months (95% CI: 5.6 to 6.0) and 5.5 months (95% CI: 4.8 to 5.6) in the necitumumab plus chemotherapy and the chemotherapy alone arms, respectively. However, there was a statistically significant improvement in OS in the necitumumab plus chemotherapy arm with a median OS of 11·5 months (95% CI: 10·4 to 12·6) vs. 9·9 months (95% CI: 8·9 to 11·1); stratified HR, 0.84 (95% CI: 0·74 to 0·96; p=0·01). In the necitumumab plus chemotherapy arm, the number of subjects with at least 1 Grade 3 or worse AE was higher (388 [72%] of 538 subjects) than in the chemotherapy alone arm (333 [62%] of 541 subjects), as was the incidence of SAEs (257 [48%] of 538 subjects vs. 203 [38%] of 541 subjects). More subjects in the necitumumab plus chemotherapy arm than in the chemotherapy alone arm had Grade 3–4 hypomagnesaemia (47 [9%] of 538 subjects vs. 6 [1%] of 541 subjects) and Grade 3 rash (20 [4%] of 538 subjects vs. 1 [<1%] of 541 subjects) [35].

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 [36]. NSCLC accounts for approximately 85% of all lung cancer cases, with 25% of these being squamous cell NSCLC.

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% [37] 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.

Molecular profiling has, however, established a definite role for EGFR- and ALK-directed therapy in a subset of non-squamous 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. However, these molecular aberrations are very uncommon in

patient with squamous cell NSCLC. Current guidelines do not recommend routine testing for EGFR and ALK in squamous cell NSCLC patients.

Compared to non-squamous NSCLC, the first-line treatment options for patients with squamous cell NSCLC are somewhat limited. Newer anti-metabolites like pemetrexed have little or no activity in squamous cell patients and anti-angiogenic therapies like bevacizumab are not used due to toxicity concerns including major pulmonary hemorrhage. A platinum-based doublet with either a taxane or gemcitabine remains the mainstay first-line therapy for chemo-naïve and recurrent patients. Recently, necitumumab in combination with gemcitabine and cisplatin was approved by the FDA based on the trial outlined in Section 4.1.4. The absolute benefit from addition of necitumumab to platinum doublet remains small and is not widely used yet due to toxicity concerns as well as the need to use cisplatin-based therapy. Newer chemotherapy combination options with better efficacy results and improved safety and tolerability outcome are needed in first-line therapy for Stage IV squamous cell NSCLC.

The current study will include patients with Stage IV squamous cell NSCLC as outlined in detail in the Section 5.1.2.

A platinum doublet with a taxane or gemcitabine is the most commonly used first-line therapy for chemo-naïve metastatic squamous NSCLC patients. Carboplatin with either paclitaxel or nab-paclitaxel is one of the accepted standard options for these patients. Based on preliminary safety and efficacy data from combination studies with pembrolizumab and other PD-L1 inhibitors, the current study will utilize the carboplatin and investigator's choice of either paclitaxel or nab-paclitaxel at approved doses as the chemo-backbone in both arms of the study.

4.2.2 Rationale for Dose Selection/Regimen/Modification

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

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

Among the 8 randomized dose-comparison studies, a total of 2262 subjects were enrolled with melanoma and NSCLC, covering different disease settings (treatment-naïve, previously treated, PD-L1 enriched, and all-comers) and different treatment settings (monotherapy and in combination with chemotherapy). Three studies compared 2 mg/kg Q3W vs. 10 mg/kg Q2W (KN001 B2, KN001 D, and KN021), and 3 studies compared 10 mg/kg Q3W vs. 10 mg/kg Q2W (KN001 B3, KN001 F2, and KN006). All of these studies demonstrated flat

dose- and exposure-response relationships across the doses studied representing an approximate 5 to 7.5 fold difference in exposure. The 2 mg/kg (or 200 mg fixed-dose) Q3W provided similar responses to the highest doses studied. Subsequently, flat dose-/exposure-response relationships were also observed in other tumor types including head and neck cancer, bladder cancer, gastric cancer, and classical Hodgkin Lymphoma, confirming 200 mg Q3W as the appropriate dose independent of the tumor type. These findings are consistent with the mechanism of action of pembrolizumab, which acts by interaction with immune cells, and not via direct binding to cancer cells.

Additionally, pharmacology data clearly show target saturation at 200 mg Q3W. First, PK data in KEYNOTE-001 evaluating TMDD conclusively demonstrated saturation of PD-1 in systemic circulation at doses much lower than 200 mg Q3W. Secondly, a physiologically-based PK analysis was conducted to predict tumor PD-1 saturation over a wide range of tumor penetration and PD-1 expression. This evaluation concluded that pembrolizumab at 200 mg Q3W achieves full PD-1 saturation in both blood and tumor.

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

4.2.2.1 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, crossover is allowed at time of documented disease progression. Due to positive interim results, subjects who are still on study intervention will be allowed to be unblinded, and subjects in the saline placebo arm will be allowed to discontinue saline placebo treatment and have the option of receiving pembrolizumab.

4.2.3 Rationale for Endpoints

4.2.3.1 Efficacy Endpoints

Primary: This trial has dual primary endpoints of PFS and OS. The trials will be considered positive if hypothesis test for either one of these primary endpoints is successful.

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 a blinded independent 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 PD will be based on the blinded independent central imaging

vendor assessment of progression, rather than local site investigator/radiology assessment. Expedited assessment by the blinded independent central imaging vendor in instances of suspected radiological progression identified at the site (verification of PD) will be communicated to the study team. The crossover arm as well as the approval of nivolumab and pembrolizumab in the second-line setting will make subject crossover to a PD-1/PD-L1 agent from the control group almost certain and may make the ability to measure OS reliably challenging. However, OS is an important endpoint in the treatment of metastatic NSCLC and this trial will evaluate both PFS and OS as dual primary endpoints as outlined in detail in Section 8.0 Statistical Analysis Plan.

Secondary: ORR by RECIST 1.1 criteria as assessed by blinded independent central radiology review and DOR by RECIST 1.1 as assessed by blinded central radiologists' review will serve as additional measures of efficacy. In a recent exploratory analysis of best RECIST response and survival in patients with metastatic squamous NSCLC treated with a PD-1 inhibitor, there was correlation between response and OS.

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 irRECIST 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.

irRECIST is RECIST 1.1 adapted to account for the unique tumor response seen with immune-therapeutics as described in [38]. The assessment of unidimensional target lesions and response categories per irRECIST are identical to RECIST 1.1. However, MSD 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 (see Section 7.1.2.6.6 for details).

4.2.3.3 Patient Reported Outcomes

4.2.3.3.1 EORTC QLQ-C30 and EORTC QLQLC13

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 5 functional dimensions (physical, role, emotional, cognitive, and social), 3 symptom items (fatigue, nausea/vomiting, and pain), 6 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) [39]. 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 [39] [40].

4.2.3.3.2 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 5 health state dimensions in this instrument include the following: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension is rated on a 3-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.

4.2.3.4 Safety Endpoints

The safety objective of this study is to characterize the safety and tolerability of pembrolizumab in combination with carboplatin and paclitaxel or nab-paclitaxel chemotherapy in subjects not previously systemically treated for squamous NSCLC. The safety analysis will be based on subjects who have toxicities as defined by the CTCAE, version 4.0.

The attribution to drug, time-of-onset, duration of the event, its resolution, and any concomitant medications administered will be recorded. AEs will be analyzed including, but not limited to, all AEs, SAEs, fatal AEs, and laboratory changes. Furthermore, specific events will be collected and designated as ECIs as described in Section 7.2.3.2.

The mandatory Safety Follow-up Visit should be conducted approximately 30 days after the last dose of study treatment or before the initiation of new anti-neoplastic treatment, whichever is earlier. All AEs that occur prior to the Safety Follow-up Visit should be recorded. Subjects with an AE of Grade >1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new anti-neoplastic therapy, whichever is earlier. SAEs that occur within 90 days following cessation of treatment or 30 days following cessation of treatment if the subject initiated new anti-neoplastic therapy, whichever is earlier, should be followed and recorded.

4.2.3.5 Planned Exploratory Biomarker Research

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

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

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

Tumor and blood RNA analyses: Both genome-wide and targeted mRNA expression profiling and sequencing in tumor tissue and in blood may be performed to define gene signatures that correlate to clinical response to treatment with pembrolizumab or other immunotherapies. Pembrolizumab induces a response in tumors that likely reflects an inflamed/ immune phenotype. Specific immune-related gene sets (such as those capturing

IFN-gamma transcriptional pathways) may be evaluated and new signatures may be identified. Individual genes related to the immune system may also be evaluated (eg, IL-10). MicroRNA profiling may also be pursued.

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

Other blood-derived biomarkers:

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

4.2.3.6 Future Biomedical Research

The Sponsor will conduct FBR on specimens for which consent was provided during this study. This research may include genetic analyses (DNA), gene expression profiling (RNA), proteomics, metabolomics (serum, plasma) and/or the measurement of other analytes, depending on which specimens are consented for FBR.

Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol and will only be conducted on specimens from appropriately consented participants. The objective of collecting/retaining specimens for FBR 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 FBR 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

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

As described in Sections 4.1.2. and 4.1.3 (preliminary) study results show that pembrolizumab in combination with chemotherapy have significant clinical activity as

first-line therapy in patients with advanced NSCLC. Considering the high unmet medical need for new and tolerable treatment options in patients with Stage IV squamous NSCLC, the anti-tumor activity and the favorable safety profiles, the existing data suggests that a combination of PD-1 blockade with chemotherapy is a promising therapeutic strategy and the benefit-risk assessment for patients included into this trial is considered to be favorable.

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

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

Male/Female subjects with squamous NSCLC who have not received prior systemic chemotherapy treatment for their metastatic NSCLC and who are at least 18 years of age will be enrolled in this trial.

5.1.2 Subject Inclusion Criteria

A participant will be eligible for inclusion in the study if the participant meets all of the following criteria:

1. Have a histologically or cytologically confirmed diagnosis of Stage IV (M1a or M1b-AJCC 7th edition) squamous NSCLC. Patients with mixed histology (example adenosquamous) are allowed if there is squamous component in the specimen.
2. 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.
3. Have not received prior systemic treatment for their 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.
4. 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.
5. Be ≥18 years of age on day of providing documented informed consent.
6. Have a life expectancy of at least 3 months.
7. Have a performance status of 0 or 1 on the Eastern Cooperative Oncology Group (ECOG) Performance Status.
8. 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	
Creatinine OR calculated creatinine clearance (CrCl)[a] (GFR can also be used in place of creatinine or CrCl)	≤1.5 X upper limit of normal (ULN) **OR** ≥60 mL/min for subjects with creatinine levels >1.5 X institutional ULN
Hepatic	
Serum total bilirubin	≤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 × ULN unless subject is receiving anticoagulant therapy as long as PT or aPTT is within therapeutic range of intended use of anticoagulants
[a.] Creatinine Clearance should be calculated per institutional standard	

9. 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.
10. 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 pembrolizumab or 180 days after the last dose of chemotherapy, whichever is longer.

    Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject.
11. 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 chemotherapy through 95 days after the last dose of chemotherapy. If male subject with a pregnant partner(s), must agree to use a condom starting with the first dose of chemotherapy through 95 days after the last dose of

chemotherapy; 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.

12. Subject (or legally acceptable representative) has provided documented 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 participant must be excluded from the study if the participant meets any of the following criteria:

1. Has non-squamous histology NSCLC. Mixed tumors will be categorized by the predominant cell type. If small cell elements are present, the subject is ineligible. For non-small cell histology, if there is any squamous element present (example adenosquamous), the subject is eligible; the squamous element does not have to be predominant.
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 other targeted or biological antineoplastic therapy (eg, 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 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.

9. 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 asymptomatic brain metastases (ie, no neurological symptoms, no requirements for corticosteroids, and no lesion >1.5 cm) may participate but will require regular imaging of the brain as a site of disease.
10. Has pre-existing peripheral neuropathy that is ≥Grade 2 by Common Terminology Criteria for Adverse Events (CTCAE), version 4.
11. Previously had a severe hypersensitivity reaction to treatment with another monoclonal antibody.
12. Has a known sensitivity to any component of carboplatin or paclitaxel or nab-paclitaxel.
13. Has active autoimmune disease that has required systemic treatment in past 2 years (ie, with use of disease-modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid-replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.
14. Is on chronic systemic steroids. Subjects with asthma who require intermittent use of bronchodilators, inhaled steroids, or local steroid injections would not be excluded from the study.
15. Had prior treatment with any other anti-PD-1, PD-L1, or PD-L2 agent or an antibody or a small molecule targeting other immuno-regulatory receptors or mechanisms. Has participated in any other pembrolizumab trial and has been treated with pembrolizumab.

    Examples of such antibodies include (but are not limited to) antibodies against IDO, PD-L1, IL-2R, GITR.
16. Has an active infection requiring therapy.
17. Has known history of human immunodeficiency virus (HIV) (known HIV 1/2 antibodies positive).
18. 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.
19. 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.

20. Has known psychiatric or substance abuse disorder that would interfere with cooperation with the requirements of the trial.
21. Is, at the time of providing documented informed consent, a regular user (including "recreational use") of any illicit drugs or had a recent history (within the last year) of substance abuse (including alcohol).
22. Has interstitial lung disease or a history of pneumonitis that required oral or intravenous glucocorticoids to assist with management. Lymphangitic spread of the NSCLC is not exclusionary.
23. Removed.

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

Arm Name	Arm Type	Intervention Name	Intervention Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/Treatment Period/ Vaccination Regimen	Use	IMP or NIMP/ AxMP	Sourcing
Arm 1	Experimental	Pembrolizumab	Biological/ Vaccine	Solution for Infusion	25 mg/mL	200 mg	IV Infusion	Q3W for up to 35 cycles	Test Product	IMP	Provided centrally by the Sponsor
Arm 1	Experimental	Paclitaxel	Drug	Per Approved Product Label	Per Approved Product Label	200 mg/m^2	IV Infusion	Q3W for up to 4 cycles	Background Treatment	NIMP/ AxMP	Provided centrally by the Sponsor or locally sourced
Arm 1	Experimental	Nab-paclitaxel	Drug	Per Approved Product Label	Per Approved Product Label	100 mg/m^2	IV Infusion	Q1W for up to 4 cycles	Background Treatment	NIMP/ AxMP	Provided centrally by the Sponsor or locally sourced
Arm 1	Experimental	Carboplatin	Drug	Per Approved Product Label	Per Approved Product Label	AUC 6 mg/mL/ min	IV Infusion	Q3W for up to 4 cycles	Background Treatment	NIMP/ AxMP	Provided centrally by the Sponsor or locally sourced
Arm 2	Placebo Comparator	Saline Placebo	Drug	Solution of Infusion	NA	NA	IV Infusion	Q3W for up to 35 cycles	Placebo	IMP	Locally sourced

Arm Name	Arm Type	Intervention Name	Intervention Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/Treatment Period/ Vaccination Regimen	Use	IMP or NIMP/ AxMP	Sourcing
Arm 2	Placebo Comparator	Paclitaxel	Drug	Per Approved Product Label	Per Approved Product Label	200 mg/m^2	IV Infusion	Q3W for up to 4 cycles	Background Treatment	NIMP/ AxMP	Provided centrally by the Sponsor or locally sourced
Arm 2	Placebo Comparator	Nab-paclitaxel	Drug	Per Approved Product Label	Per Approved Product Label	100 mg/m^2	IV Infusion	Q1W for up to 4 cycles	Background Treatment	NIMP/ AxMP	Provided centrally by the Sponsor or locally sourced
Arm 2	Placebo Comparator	Carboplatin	Drug	Per Approved Product Label	Per Approved Product Label	AUC 6 mg/mL/ min	IV Infusion	Q3W for up to 4 cycles	Background Treatment	NIMP/ AxMP	Provided centrally by the Sponsor or locally sourced

AUC=area under the curve; EEA=European Economic Area; IMP=investigational medicinal product; IV=intravenous; NIMP/AxMP=noninvestigational/auxiliary medicinal product; Q1W=once every week; Q3W=once every 3 weeks.

The classification of IMP and NIMP/AxMP in this table is based on guidance issued by the European Commission and applies to countries in the EEA. Country differences with respect to the definition/classification of IMP and NIMP/AxMP may exist. In these circumstances, local legislation is followed.

In this protocol, placebo for pembrolizumab is diluent alone (normal saline); diluent is used for blinding purposes and does not contain active ingredients.

Other current or former names or aliases for pembrolizumab are as follows: MK-3475.

Pembrolizumab/saline placebo to be administered prior to chemotherapy.

Investigator's choice of either paclitaxel or nab-paclitaxel.

Carboplatin daily dose should not exceed 900 mg.

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 is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product as per local guidelines unless otherwise instructed by the Sponsor.

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

5.2.1 Dose Selection/Modification

5.2.1.1 Dose Selection (Preparation)

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

Standard chemotherapeutic agents (carboplatin and paclitaxel or nab-paclitaxel) will be prepared and administered as per the approved product label.

5.2.1.2 Dose Modification (Escalation/Titration/Other)

If appropriate, the investigator may attribute each toxicity event to carboplatin, paclitaxel or nab-paclitaxel or pembrolizumab alone or to the combination and use a stepwise dose reduction. Dose modifications must be based on the maximum toxicity experienced during a cycle. Treatment-related toxicity must resolve to Grade ≤1 or baseline prior to resuming the subsequent cycle, with the exception of alopecia, Grade 2 fatigue, endocrine-related AEs requiring treatment or hormone replacement, which may be Grade ≤2. Dose modifications and toxicity management guidelines for immune-related AEs associated with pembrolizumab are outlined in Section 5.2.1.2.2 and Table 3 below. 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 third dose modification to any particular component will have that agent discontinued.

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 third dose modification to any particular component will have that agent discontinued.

Pembrolizumab dose reductions are not permitted. Pembrolizumab treatment may be interrupted or discontinued due to toxicity.

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 3 agents, all 3 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 during the first 4 cycles if appropriate.

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

The CTCAE, version 4.0 must be used to grade the severity of AEs. All dose modifications should be based on the AE requiring the greatest dose modification.

5.2.1.2.1 Carboplatin and Paclitaxel or Nab-paclitaxel Chemotherapy Regimen

Refer to approved product labels for dose modifications regarding this regimen.

5.2.1.2.2 Immune-Related Events and Dose Modification (Withhold, Treat, Discontinue

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

AEs associated with pembrolizumab exposure may represent an immune-related response. These irAEs may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study 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 monotherapy, coformulations, or IO combinations are provided in Table 3.

Table 3 Dose Modifications and Toxicity Management Guidelines for Immune-related Adverse Events Associated with Pembrolizumab Monotherapy, Coformulations or IO Combinations

General instructions:

1. Severe and life-threatening irAEs should be treated with IV corticosteroids followed by oral steroids. Other immunosuppressive treatment should begin if the irAEs are not controlled by corticosteroids.
2. Pembrolizumab monotherapy, coformulations or IO combinations must be permanently discontinued if the irAE does not resolve or the corticosteroid dose is not ≤10 mg/day within 12 weeks of the last treatment.
3. The corticosteroid taper should begin when the irAE is ≤ Grade 1 and continue at least 4 weeks.
4. If pembrolizumab monotherapy, coformulations or IO combinations have been withheld, treatment may resume after the irAE decreased to ≤ Grade 1 after corticosteroid taper.

irAEs	Toxicity Grade (CTCAEv4.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper • Add prophylactic antibiotics for opportunistic infections	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment
	Recurrent Grade 2 or Grade 3 or 4	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.
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

irAEs	Toxicity Grade (CTCAEv4.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
AST / ALT Elevation or Increased Bilirubin	Grade 2 [a]	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 [b] or 4 [c]	Permanently discontinue	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	
T1DM or Hyperglycemia	New onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold [d]	• 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 [d]		
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 [d]		

irAEs	Toxicity Grade (CTCAEv4.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Hypothyroidism	Grade 2-4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care	• Monitor for signs and symptoms of thyroid disorders
Nephritis and renal dysfunction	Grade 2	Withhold	• Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Asymptomatic cardiac enzyme elevation with clinical suspicion of myocarditis (which was previously myocarditis Grade 1 using CTCAE v4.0)	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 2, 3 or 4	Permanently discontinue		
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Confirmed SJS, TEN, or DRESS	Permanently discontinue		

irAEs	Toxicity Grade (CTCAEv4.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
All Other irAEs	Persistent Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 3	Withhold or discontinue [e]		
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

AE(s)=adverse event(s); ALT= alanine aminotransferase; AST=aspartate aminotransferase; CTCAE=Common Terminology Criteria for Adverse Events; DRESS=Drug Rash with Eosinophilia and Systemic Symptom; GI=gastrointestinal; IO=immuno-oncology; ir=immune related; IV=intravenous; SJS=Stevens-Johnson Syndrome; T1DM=type 1 diabetes mellitus; TEN=Toxic Epidermal Necrolysis; ULN=upper limit of normal.

Note: Non-irAE will be managed as appropriate, following clinical practice recommendations.

[a] AST/ALT: >3.0 to5.0 x ULN if baseline normal; >3.0 to 5.0 x baseline, if baseline abnormal; bilirubin:>1.5 to 3.0 x ULN if baseline normal; >1.5 to 3.0 x baseline if baseline abnormal.

[b] AST/ALT: >5.0 to 20.0 x ULN, if baseline normal; >5.0 to 20.0 x baseline, if baseline abnormal; bilirubin:>3.0 to 10.0 x ULN if baseline normal; >3.0 to 10.0 x baseline if baseline abnormal.

[c] AST/ALT: >20.0 x ULN, if baseline normal; >20.0 x baseline, if baseline abnormal; bilirubin: >10.0 x ULN if baseline normal; >10.0 x baseline if baseline abnormal.

[d] The decision to withhold or permanently discontinue pembrolizumab monotherapy, coformulations or IO combinations is at the discretion of the investigator or treating physician. If control achieved or ≤ Grade 2, pembrolizumab monotherapy, coformulations or IO combinations may be resumed.

[e] Events that require discontinuation include, but are not limited to: encephalitis and other clinically important irAEs (eg, vasculitis and sclerosing cholangitis).

Dose Modification and Toxicity Management of Infusion Reactions Related to Pembrolizumab Monotherapy, Coformulations, or IO Combinations

Pembrolizumab monotherapy, coformulations, or IO combinations 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 monotherapy, coformulations, or IO combinations associated infusion reactions are provided in Table 4.

Table 4 Pembrolizumab Monotherapy, Coformulations or IO Combinations 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 participant is deemed medically stable in the opinion of the investigator	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 h	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 participant 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 (eg, from 100 mL/h to 50 mL/h). Otherwise dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose. Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study intervention.	Participant may be premedicated 1.5 h (±30 min) prior to infusion of study intervention with: Diphenhydramine 50 mg PO (or equivalent dose of antihistamine). Acetaminophen 500 to 1000 mg PO (or equivalent dose of analgesic).

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 3 or 4 Grade 3: Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms after initial improvement; hospitalization indicated for other clinical sequelae (eg, 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 participant is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. Participant is permanently discontinued from further study intervention.	No subsequent dosing

h=hour; IV=intravenous; CTCAE=Common Terminology Criteria for Adverse Events; NCI=National Cancer Institute; NSAIDs=nonsteroidal anti-inflammatory drugs.

Note: 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 CTCAE v5.0 at http://ctep.cancer.gov.

Other Allowed Dose Interruption for Pembrolizumab Monotherapy, Coformulations, or IO Combinations

Pembrolizumab monotherapy, coformulations, or IO combinations may be interrupted for situations other than treatment-related AEs such as medical or surgical events and/or unforeseen circumstances not related to study intervention. However, study intervention is to be restarted within 3 weeks of the originally scheduled dose and within 42 days of the previously administered dose, unless otherwise discussed with the Sponsor. The reason for study intervention interruption is to be documented in the participant's study record.

5.2.2 Timing of Dose Administration

Subjects will receive blinded pembrolizumab 200 mg (D1) or saline placebo (D1) together with paclitaxel 200mg/m^2 (D1) OR nab-paclitaxel 100mg/m^2 (D1, D8, D15) + carboplatin

AUC 6 (D1) Q3W for 4 cycles followed by blinded pembrolizumab 200 mg (D1) or saline placebo (D1) Q3W until progression/completion. Because of positive interim results, subjects will be unblinded and will be allowed to discontinue treatment with saline placebo.

Pembrolizumab or saline will be administered prior to chemotherapy.

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 where 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 through blinded independent central imaging vendor review. Subjects for whom PD is not confirmed on subsequent imaging may resume treatment. Please see Section 5.8 for other exceptions.

5.2.2.1 Pembrolizumab/Saline Placebo

Pembrolizumab/saline placebo will be administered as a 30-minute IV infusion Q3W. Pembrolizumab/saline placebo will be administered prior to chemotherapy. 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 (ie, 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 Paclitaxel

Paclitaxel 200 mg/m^2 will be administered as an IV infusion over 3 hours Q3W for 4 cycles as per local practice and labels. All subjects should be pre-medicated with oral or IV steroids and anti-histamines according to the approved product label and/or standard practice. Additional pre-medications should be administered as per standard practice. Paclitaxel should be completely administered before initiating carboplatin dose.

5.2.2.3 Nab-paclitaxel

Nab-paclitaxel will be administered at 100 mg/m^2 as an IV infusion over 30 minutes for 4 cycles as per local practice and labels. Subjects will be dosed on Day 1, 8 and 15 of each Q3W cycle. Nab-paclitaxel should be completely administered before initiating carboplatin dose.

5.2.2.4 Carboplatin

Carboplatin AUC 6 mg/mL/min will be administered as an IV infusion over 15-60 minutes Q3W for 4 cycles immediately after paclitaxel or nab-paclitaxel as per local practice and labels. The carboplatin dose should be calculated using Calvert formula (see below). Carboplatin dose should not exceed 900 mg.

Calvert Formula:

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

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

Maximum carboplatin dose (mg) = target AUC 6 (mg•min/mL) x (125 + 25) = 6 x 150 mL/min = 900 mg

5.2.2.5 Antiemetic Therapy

Antiemetic therapy should follow MASCC guidelines (http://www.mascc.org/antiemetic-guidelines/) and should, for the first 4 cycles, include a 5-HT3 receptor antagonist, dexamethasone (or equivalent), and/or aprepitant as per the MASCC guidelines. If aprepitant is not locally available, the Sponsor will provide supplies.

5.2.3 Trial Blinding

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 IVRS/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.

Because of positive interim results, this study is being unblinded so that subjects assigned to the placebo arm (Arm 2) may discontinue treatment with normal saline placebo and have the option of receiving pembrolizumab if there is documented progressive disease by central radiological review. Thus, the subject, investigator, and Sponsor personnel or delegate(s) who are involved in the treatment administration or clinical evaluation of the subjects will be made aware of the group assignments.

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

5.3 Randomization or Treatment Allocation

Treatment allocation/randomization will occur centrally using an interactive voice response system / integrated web response system (IVRS/IWRS). There are 2 treatment arms. Subjects will be assigned randomly in a 1:1 ratio to pembrolizumab and chemotherapy or saline placebo and chemotherapy, respectively. The choice of paclitaxel or nab-paclitaxel treatment will be determined prior to randomization and documented in the IVRS/IWRS.

5.4 Stratification

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

1) PD-L1 expression: TPS ≥1% vs. <1%. PD-L1 non-evaluable subjects will be included with the TPS <1% group.
2) Choice of taxane chemotherapy: paclitaxel vs. nab-paclitaxel.
3) Geographic region of the enrolling site (East Asia vs. non-East Asia).

5.5 Concomitant Medications/Vaccinations (Allowed & Prohibited)

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

5.5.1 Acceptable Concomitant Medications

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

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

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

Colony-Stimulating Factors

Routine use of CSFs is not permitted. American Society of Clinical Oncology guidelines for use of CSFs should be followed [41].

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 with Sponsor's approval.
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chickenpox, yellow fever, nasal seasonal flu, nasal H1N1 flu, rabies, BCG, and typhoid.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an immune-related adverse Event (as listed in Section 5.6) or for use as a pre-medication for chemotherapeutic agents specified in the protocol or as a pre-medication prior to a CT scan for subjects with contrast allergy or for use for COPD exacerbation requiring steroid for recovery. Replacement doses of steroids (for example, prednisone 10 mg daily) are permitted while on study.

  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 treatment. 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

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

Note: If after the evaluation the event is determined not to be related, the investigator does not need to follow the treatment guidance (as outlined below). Refer to Table 3 in Section 5.2.1 for guidelines regarding dose modification and supportive care.

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.

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

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

(1) postmenopausal (defined as at least 12 months with no menses without an alternative medical cause; in women <45 years of age a high 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 subjects of childbearing potential must agree to avoid becoming pregnant while receiving study intervention and for 120 days after the last dose of pembrolizumab or 180 days after the last dose of chemotherapy, whichever is longer, and male subjects of reproductive potential must agree to avoid impregnating a partner while receiving chemotherapy through 95 days after the last dose of chemotherapy, 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 (eg, 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 intervention may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study, female subjects of childbearing potential must adhere to the contraception requirement (described above) from the day of study intervention initiation (or 14 days prior to the initiation of study intervention for oral contraception) throughout the study period up to 120 days after the last dose of pembrolizumab or 180 days after the last dose of chemotherapy, whichever is longer and male subjects of reproductive potential must adhere to the contraception requirement (described above) starting with the first dose of chemotherapy through 95 days after the last dose of chemotherapy. If there is any question that a subject of childbearing or reproductive potential will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

5.7.3 Use in Pregnancy

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

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. Discontinuation from the treatment is permanent except for 1) a subject who discontinued

treatment for CR or 2) a subject who discontinued after receiving the maximum 35 pembrolizumab/saline placebo treatment. These last 2 categories of subjects may be allowed to begin treatment again if deemed medically appropriate in the second course phase (re-treatment).

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

- The subject or legal representative (such as a parent or legal guardian) withdraws consent.
- The subject is lost to follow-up.

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

- Unacceptable adverse experiences as described in Section 5.2.1.2.
- Completed a total of 35 treatments of pembrolizumab/saline placebo. Subjects are allowed to discontinue saline placebo.
- Documented disease progression.

  Note: If a subject has PD verified by central radiological review using RECIST 1.1, the subject may be unblinded. If a subject was receiving saline placebo and meets all crossover criteria defined in Section 7.1.5.6, he/she will have the opportunity to crossover to receive open-label pembrolizumab monotherapy. If a subject was receiving pembrolizumab and is deemed to be clinically benefiting despite radiological progression they will have the opportunity to continue open-label pembrolizumab monotherapy. If a subject has unconfirmed PD and is clinically stable, it is at the discretion of the investigator to continue treating the subject with the assigned treatment per protocol until PD is confirmed at least 28 days from the date of the scan suggesting PD.

  Clinical Stability is defined as:

  - Absence of symptoms and signs indicating clinically significant progression of disease (including worsening of laboratory values) indicating disease progression.
  - No decline in ECOG performance status.
  - Absence of rapid progression of disease or progressive tumor at critical anatomical sites (eg, cord compression) requiring urgent alternative medical intervention.
- Intercurrent illness that prevents further administration of treatment.
- Investigator's decision to withdraw the subject from treatment.
- The subject has a confirmed positive serum pregnancy test.
- Noncompliance with trial treatment or procedure requirements.
- Administrative reasons.

If a subject attains CR verified by central radiological review, has been treated for at least 8 cycles of study treatment, and has at least 2 cycles of study treatment beyond the date when

the initial CR was declared OR the subject has received the maximum administrations of pembrolizumab/saline placebo as outlined above, the subject and investigator may consider stopping therapy with pembrolizumab/saline placebo. Subjects who discontinue pembrolizumab/saline placebo and then experience radiographic PD by local investigator's assessment according to irRECIST may be eligible for re-treatment with pembrolizumab in the Second Course Phase at the discretion of the investigator as described in Section 7.1.5.5.

Chemotherapy will be discontinued when a subject has received the maximum number of 4 cycles as outlined in the protocol.

The End of Treatment and Follow-up visit procedures are listed in Section 6.0 - 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 AE monitoring even if the subject started new antineoplastic treatment (SAEs 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.

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

5.9 Subject Replacement Strategy

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

5.10 Beginning and End-of-Study Definition

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

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

5.11 Clinical Criteria for Early Trial Termination

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

6.1.1 Initial Treatment Phase – Cycles 1-4

Details regarding procedures listed in this table are outlined in Section 7.

	Screening Phase	Treatment Cycles (3-Week Cycles)											
Treatment Cycle	**Screening (Visit 1)**	**1**	**1**	**1**	**2**	**2**	**2**	**3**	**3**	**3**	**4**	**4**	**4**
Day (in Cycle)		**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**
Scheduling Window (Days):[1]	**-28 to -1**	**+3**	**± 1**	**± 1**	**± 3**	**± 1**	**± 1**	**± 3**	**± 1**	**± 1**	**± 3**	**± 1**	**± 1**
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		
NSCLC Disease Details and Prior Treatment	X												
Call IVRS		X	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]
Clinical Procedures / Assessments													
Review Adverse Events		X	X[3]	X[3]	X	X[3]	X[3]	X	X[3]	X[3]	X	X[3]	X[3]
Full Physical Examination	X												
Directed Physical Examination		X			X			X			X		
Vital Signs and Weight	X[4]	X	X[3]	X[3]	X	X[3]	X[3]	X	X[3]	X[3]	X	X[3]	X[3]
12-Lead ECG	X												
ECOG Performance Status	X[5]	X			X			X			X		

	Screening Phase	Treatment Cycles (3-Week Cycles)											
Treatment Cycle	**Screening (Visit 1)**	**1**	**1**	**1**	**2**	**2**	**2**	**3**	**3**	**3**	**4**	**4**	**4**
Day (in Cycle)		**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**
Scheduling Window (Days):[1]	**-28 to -1**	**+3**	**± 1**	**± 1**	**± 3**	**± 1**	**± 1**	**± 3**	**± 1**	**± 1**	**± 3**	**± 1**	**± 1**
Laboratory Procedures / Assessments: Analysis Performed by Local Laboratory													
Pregnancy Test - Urine or Serum β-HCG [6]	X	X			X			X			X		
PT/INR and aPTT/PTT	X[5]												
CBC with Differential [7]	X[5]		X[3,8]	X[2,8]	X	X[3,8]	X[3,8]	X	X[3,8]	X[3,8]	X	X[3,8]	X[3,8]
Comprehensive Chemistry Panel[5,7]	X[5]				X			X			X		
Urinalysis[7]	X[5]												
T3 or FT3, FT4 and TSH [7,9]	X[5]				X						X		
Analysis Performed by Central Laboratory													
Blood for Genetic Analysis[10]		X											
Blood for RNA Analyses		X			X								
Blood for Plasma Biomarker Analyses		X			X								
Blood for Serum Biomarker Analyses		X			X								
Tumor Tissue Collection													
Tumor Tissue Collection	X												
Efficacy Measurements													
Tumor Imaging	X							X[11]					
Study Drug Administration													
Carboplatin		X			X			X			X		
Paclitaxel		X			X			X			X		
Nab-paclitaxel[12]		X	X	X	X	X	X	X	X	X	X	X	X
Pembrolizumab or Saline Placebo[13]		X			X			X			X		
Patient Reported Outcomes (PRO)[14]													
EuroQol (EQ)-5D1		X			X			X			X		
EORTC QLQ-C30		X			X			X			X		
EORTC QLQ-LC13		X			X			X			X		

	Screening Phase	Treatment Cycles (3-Week Cycles)											
Treatment Cycle	**Screening (Visit 1)**	**1**	**1**	**1**	**2**	**2**	**2**	**3**	**3**	**3**	**4**	**4**	**4**
Day (in Cycle)		**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**
Scheduling Window (Days):[1]	**-28 to -1**	**+3**	**± 1**	**± 1**	**± 3**	**± 1**	**± 1**	**± 3**	**± 1**	**± 1**	**± 3**	**± 1**	**± 1**

1. In general, the window for each visit is ± 3 days unless otherwise noted. If treatment cycles are adjusted all procedures except imaging will be completed according to the cycle number and not weeks on treatment, imaging will not be adjusted for delays in treatment cycles and will be performed per calendar schedule.
2. On Cycle 1, Day 1, call to obtain allocation number. At subsequent visits, call to ensure visits are captured in the IVRS system.
3. Visit Day 8 and Day 15 procedures only apply to subjects receiving nab-paclitaxel.
4. Height will be measured only at Visit 1.
5. ECOG and laboratory tests for screening are to be performed within 10 days prior to the first dose of trial treatment.
6. For women of reproductive potential, a urine pregnancy test should be performed within 72 hours prior to first dose of each cycle of trial treatment. A serum test can be considered if urine is not appropriate.
7. After Cycle 1, lab samples can be collected up to 3 days prior to Day 1 of subsequent cycles.
8. If subject received nab-paclitaxel, labs are drawn in conjunction with each dose of nab-paclitaxel on Day 8 and Day 15 of each Q3W cycle.
9. Subjects may be dosed in subsequent cycles after Cycle 1, Day 1 while thyroid function tests are pending.
10. 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 FBR if the participant (or their legally acceptable representative) provides documented informed consent for FBR. 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.
11. Imaging is performed at Week 6 (± 7 days), Week 12 (± 7 days), and Week 18 (± 7 days) then every 9 weeks (63 days ± 7 days) for the first 45 weeks in the treatment period. Refer to imaging manual for additional details.
12. Dosing for nab-paclitaxel is on Day 1, Day 8, and Day 15 of each Q3W.
13. Subjects assigned to the placebo arm (Arm 2) may discontinue treatment with saline placebo and have the option of receiving pembrolizumab if there is documented progressive disease by central radiological review.
14. PROs (EQ-5D, EORTC QLQ-C30, and EORTC QLQ-LC13) are completed at Cycles 1 through 7 and then every third cycle (every 9 weeks) while on treatment up to 48 weeks.

6.1.2 Initial Treatment Phase – Cycles 5 and Beyond

Details regarding procedures listed in this table are outlined in Section 7.

	Treatment Cycles (3-Week Cycles)					End of Treatment	Post Treatment
Treatment Cycle	**5**	**6 to 17**	**18 to 35**	**Discon**	**Safety Follow-up**	**Follow-up Visits**	**Survival Follow-up[1]**
Scheduling Window (Days):[2]	**± 3**	**± 3**	**± 3**	**At Time of Discon± 3 days**	**30 Days Post Dose+ 7 days**	**6 Weeks Post Safety Follow-up± 3 days**	**Every 12 Weeks± 7 days**
Prior and Concomitant Medications	X	X	X	X	X	X	X
Subsequent antineoplastic therapy status				X	X	X	X
Survival Status[3]	◄	———	►		◄	———	► X
Clinical Procedures / Assessments							
Review Adverse Events	X	X	X	X	X	X[4]	
Full Physical Exam				X			
Directed Physical Examination	X	X	X				
Vital Signs and Weight[5]	X	X	X	X	X		
ECOG Performance Status	X	X	X	X	X		
Laboratory Procedures / Assessments: Analysis Performed by Local Laboratory							
Pregnancy Test - Urine or Serum β-HCG	X[6]						
CBC with Differential [7]	X	X	X	X	X		
Comprehensive Chemistry Panel[7]	X	X	X	X	X		
Urinalysis[7]		X[8]	X[8]		X		
T3 or FT3, FT4 and TSH [7,9]		X[10]	X[10]		X		
Analysis Performed by Central Laboratory							
Blood for RNA Analyses	X			X			
Blood for Plasma Biomarker Analyses				X			
Blood for Serum Biomarker Analyses				X			
Efficacy Measurements							
Tumor Imaging	X[11]	X[11]	X[12]	X[13]		X[13,14]	
Study Drug Administration							
Pembrolizumab or Saline Placebo[15]	X	X	X				

	Treatment Cycles (3-Week Cycles)					End of Treatment	Post Treatment
Treatment Cycle	**5**	**6 to 17**	**18 to 35**	**Discon**	**Safety Follow-up**	**Follow-up Visits**	**Survival Follow-up[1]**
Scheduling Window (Days):[2]	**± 3**	**± 3**	**± 3**	**At Time of Discon± 3 days**	**30 Days Post Dose+ 7 days**	**6 Weeks Post Safety Follow-up± 3 days**	**Every 12 Weeks± 7 days**
Patient Reported Outcomes (PRO)[16]							
EuroQol (EQ)-5D	X	X		X	X		
EORTC QLQ-C30	X	X		X	X		
EORTC QLQ-LC13	X	X		X	X		

1. After documented disease progression, or the start of new anticancer therapy; contacts are every 12 weeks by telephone.
2. In general, the window for each visit is ± 3 days unless otherwise noted.
3. After documented local site assessed disease progression, or the start of new anticancer treatment; contacts are approximately every 12 weeks by telephone. Updated survival status may be requested by the Sponsor at any time during the course of the study. Upon Sponsor notification, all 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 that have a death event previously recorded).
4. Serious adverse events must be reported up to 90 days following cessation of treatment or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier.
5. Height will be measured only at Visit 1.
6. For women of reproductive potential, a urine pregnancy test should be performed within 72 hours prior to first dose of each cycle of trial treatment. A serum test can be considered if urine is not appropriate.
7. After Cycle 1, lab samples can be collected up to 3 days prior to Day 1 of subsequent cycles.
8. To be repeated every 6 cycles beginning with Cycle 6.
9. Subjects may be dosed in subsequent cycles after Cycle 1, Day 1 while thyroid function tests are pending.
10. To be repeated every other cycle beginning with Cycle 6.
11. Imaging is performed at Week 6 (± 7 days), Week 12 (± 7 days), and Week 18 (± 7 days) then every 9 weeks (63 days ± 7 days) for the first 45 weeks in the treatment period. Refer to imaging manual for additional details.
12. Imaging performed every 12 weeks (84 days ± 7 days) subsequently. Refer to imaging manual for additional details.
13. 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 every 12 weeks (84 ± 7 days), refer to Section 7.1.2.6.3.
14. In subjects who discontinue trial treatment, tumor imaging should be performed at the time of treatment discontinuation (± 4 week window).
15. Subjects assigned to the placebo arm (Arm 2) may discontinue treatment with saline placebo and have the option of receiving pembrolizumab if there is documented progressive disease by central radiological review.
16. PROs (EQ-5D, EORTC QLQ-C30, and EORTC QLQ-LC13) are completed at Cycles 1 through 7 and then every third cycle (every 9 weeks) while on treatment up to 48 weeks. All PROs are also completed at treatment discontinuation visit and 30-day safety follow-up visit.

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:	**1**	**2**	**3**	**4**	**To be Repeated Beyond 6 Cycles** **5**	**6**	**Discon**	**Safety Follow-up[1]**	**Follow-Up Visits**	**Survival Follow-up[1]**
Scheduling Window (Days)[2]:	**+3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At Time of Discon± 3 days**	**30 Days Post Discon + 7 days**	**6 Weeks Post Safety Follow-up± 3 days**	**Every 12 Weeks± 7 days**
Administrative Procedures										
Eligibility Criteria	X									
Concomitant Medication Review	X	X	X	X	X	X	X	X		
Subsequent antineoplastic therapy status							X	X	X	X
Survival Status[3]	◄					►		◄	►	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			
Vital Signs	X	X	X	X	X	X	X			
ECOG Performance Status	X	X	X	X	X	X	X	X		
Laboratory Procedures/Assessments: analysis performed by LOCAL laboratory										
Pregnancy Test – Serum or Urine	X[4]									
Hematology[5]	X[6]	X	X	X	X	X	X	X		
Chemistry Panel[5]	X[6]	X	X	X	X	X	X	X		
Urinalysis[5]	X[6]		X			X[8]				
T3 or FT3, FT4, TSH[5,7]	X[6]		X			X[9]		X		
Efficacy Measurements										
Tumor Imaging	X[10]				X[11]	X[11]	X		X[11]	

Trial Period:	Treatment Cycles (3-Week Cycles)						End of Treatment	Post-Treatment		
Treatment Cycle/Title:	1	2	3	4	To be Repeated Beyond 6 Cycles 5	6	Discon	Safety Follow-up[1]	Follow-Up Visits	Survival Follow-up[1]
Scheduling Window (Days)[2]:	+3	± 3	± 3	± 3	± 3	± 3	At Time of Discon± 3 days	30 Days Post Discon + 7 days	6 Weeks Post Safety Follow-up± 3 days	Every 12 Weeks± 7 days
Study Drug Administration										
Pembrolizumab	X	X	X	X	X	X				

1. After documented disease progression, or the start of new anticancer therapy; contacts are every 12 weeks by telephone.
2. In general, the window for each visit is ± 3 days unless otherwise noted.
3. After documented local site assessed disease progression, or the start of new anticancer treatment; contacts are approximately every 12 weeks by telephone. Updated survival status may be requested by the Sponsor at any time during the course of the study. Upon Sponsor notification, all 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 that have a death event previously recorded).
4. For women of reproductive potential, a serum pregnancy test should be performed within 72 hours prior to first dose of each cycle of trial treatment. A urine test can be considered if serum is not appropriate.
5. After Cycle 1, lab samples can be collected up to 3 days prior to the scheduled time point.
6. Laboratory tests for determining eligibility for retreatment are to be performed within 10 days prior to the first retreatment dose of pembrolizumab.
7. Subjects may be dosed in subsequent cycles after Cycle 1, Day 1 while thyroid function tests are pending.
8. To be repeated every 6 cycles beginning with Cycle 6.
9. To be repeated every other cycle beginning with Cycle 6.
10. A scan must be performed within 28 days prior to restarting treatment with pembrolizumab.
11. Imaging performed every 12 weeks (84 ± 7 days) from the date of re-treatment.

6.3 Crossover Phase

Applicable for subjects who are unblinded after verification for PD by blinded independent central radiological review and eligible and qualified for the crossover phase. Details regarding the procedures listed in this table are outlined in Section 7.0. Crossover subjects may receive up to 35 cycles (approximately 2 years) of pembrolizumab therapy.

	Scr Phase	Treatment Cycles[1]													End of Treatment Phase		Follow-up Phase[2]	Survival Follow-up[3]
Treatment Cycle / Scheduled Time	**Scr (Visit 1)**	**1[4]**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14 through 35**	**Discontinuation Visit[5]**	**Safety Follow-up Visit [6]**	**Follow-up Visit 3 and Beyond**	**Survival Follow-up Visit 1 and Beyond**
Scheduling Window (Days):	**-28 to -1**	**+3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**±3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At Study Drug Discontinuation± 3**	**30 Days From Last Dose+ 7**	**Every 3 Months After Visit 2± 3**	**Every 3 Months ± 7**
Administrative Procedures																			
Prior and Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Subsequent antineoplastic therapy status																X	X	X	X
Survival Status[7]	◄	———	———	———	———	———	———	———	———	———	———	———	———	———	——►		◄	———	——► X
Clinical Procedures / Assessments																			
Review Adverse Events [8]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Full Physical Examination	X	X														X	X		
Directed Physical Examination	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Vital Signs and Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
ECOG Performance Status	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Laboratory Procedures / Assessments: analysis performed by local laboratory[9]																			
CBC with Differential	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
PT/INR and aPTT/PTT	X	X																	
Comprehensive Chemistry Panel	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Urinalysis	X	X				X				X				X	X[10]	X	X		
T3 or FT3, FT4 and TSH[11]	X	X	X		X		X		X		X		X		X	X	X		
Pregnancy Test – Serum or Urine	X	X[12]																	
Efficacy Measurements																			
Tumor Imaging[13]	X	X				X				X				X	X	X	X	X[14]	
Study Drug Administration																			
Pembrolizumab[15]		X	X	X	X	X	X	X	X	X	X	X	X	X	X				

	Scr Phase	Treatment Cycles[1]													End of Treatment Phase		Follow-up Phase[2]	Survival Follow-up[3]
Treatment Cycle / Scheduled Time	**Scr (Visit 1)**	**1[4]**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14 through 35**	**Discontinuation Visit[5]**	**Safety Follow-up Visit [6]**	**Follow-up Visit 3 and Beyond**	**Survival Follow-up Visit 1 and Beyond**
Scheduling Window (Days):	**-28 to -1**	**+3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**±3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At Study Drug Discontinuation± 3**	**30 Days From Last Dose+ 7**	**Every 3 Months After Visit 2± 3**	**Every 3 Months ± 7**

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. Subjects who stop pembrolizumab after 35 trial treatments and have achieved PR and/or SD OR have achieved a CR (see Section 5.8) 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 the 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 start of a new antineoplastic therapy, whichever is earlier.
3. 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 every 3 months to assess for survival status. Post-study treatments and the subject's response to them will also be collected.
4. Screening procedures may be completed during these 30 days. All procedures and assessments completed at the time of withdrawal from the main study may be used as appropriate for the start of the Crossover Phase of the study. If subjects continue into the Crossover phase, Safety follow-up is not required.
5. The Discontinuation Visit should occur at the time study drug is discontinued for any reason. If the Discontinuation Visit occurs 30 days from the last dose of study treatment, at the time of the mandatory Safety Follow-up Visit, procedures do not need to be repeated.
6. The mandatory Safety Follow-up Visit for all subjects should be conducted approximately 30 days after the last dose of trial treatment or before the initiation of new antineoplastic treatment, whichever is earlier. 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 is earlier. Subjects who are eligible for treatment with pembrolizumab during the Second Course Phase may have up to 3 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.
7. After documented local site assessed disease progression, or the start of new anticancer therapy; 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 that have a death event previously recorded).
8. 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. After this time, report only SAEs that are considered related to trial treatment.
9. 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 14. 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.
10. Urinalysis is performed every 6 cycles after Cycle 13. Urinalysis is not required at Cycle 14.
11. Subjects may be dosed in subsequent cycles after Cycle 1, Day 1 while thyroid function tests are pending.
12. For women of reproductive potential, a serum pregnancy test should be performed within 72 hours prior to first dose of each cycle of trial treatment. A urine test can be considered if serum is not appropriate.
13. Blinded independent 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 a new anticancer therapy. Refer to imaging manual for additional details. 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, ie, immune-related RECIST or standard RECIST 1.1 on the discontinuation form.
14. Tumor imaging is not needed for subjects who start a new anticancer therapy regimen.
15. Pembrolizumab can be administered for up to 35 cycles.

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 medically qualified designee (consistent with local requirements) must obtain documented informed consent from each potential participant (or their legally acceptable representative) prior to participating in this clinical study or FBR. If there are changes to the participant's status during the study (eg, health or age of majority requirements), the investigator or medically qualified designee must ensure the appropriate documented informed consent is in place.

7.1.1.1.1 General Informed Consent

Informed consent given by the participant or their legally acceptable representative must be documented on a consent form. The form must include the study protocol number, study protocol title, dated signature, and agreement of the participant (or his/her legally acceptable representative) and of the person conducting the consent discussion.

A copy of the signed and dated informed consent form should be given to the participant (or their legally acceptable representative) before participation in the study.

The initial ICF, any subsequent revised ICF, and any written information provided to the participant must receive the IRB/IEC's approval/favorable opinion in advance of use. The participant or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the participant's willingness to continue participation in the study. 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 participant's or the participant's legally acceptable representative's dated signature.

Specifics about the study and the study population are to be included in the study informed consent form.

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 medically qualified designee will explain the FBR consent to the participant, or the participant's legally acceptable representative, answer all of his/her questions, and obtain documented informed consent before performing any procedure related to FBR. A copy of the informed consent will be given to the participant before performing any procedure related to FBR.

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 documented informed consent. At the time of treatment allocation/randomization, site personnel will add the treatment/randomization number to the Subject Identification Card.

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

7.1.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee. Medical history will include all active conditions, and any condition diagnosed within the prior 10 years that are considered to be clinically significant by the investigator. 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 anticancer therapy 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. All medications related to reportable SAEs should be recorded as defined in Section 7.2.

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 medications 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 12.5). Toxicities will be characterized in terms including seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

An irAE may be defined as an AE 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 AE 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 6.0 - Trial Flow Chart. After the first dose of trial treatment new clinically significant abnormal findings should be recorded as AEs.

7.1.2.2.2 Directed Physical Exam

For cycles that do not required a full physical exam per the 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 12.6) at screening, prior to each cycle of trial treatment, and during the Follow -up period as specified in the Trial Flow Chart.

7.1.2.6 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. Tumor imaging should be acquired by CT (strongly

preferred) and should include the chest, abdomen and pelvis. 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 a maximum of 5 target lesions in total and 2 per organ, MSD 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 PD following local site investigator-assessed first radiologic evidence of PD. Expedited verification of radiologic PD by the central imaging vendor will be communicated to the study site and Sponsor (see Section 7.1.2.6.2). The expedited central verification of PD should be requested only when the subject is a candidate for crossover and may occur either at the first instance of PD by RECIST 1.1 or the confirmation scan ≥ 4 weeks later to confirm PD by irRECIST.

7.1.2.6.1 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, ie, without evidence of progression by imaging during screening; (confirmed by MRI if MRI was used at prior imaging, or confirmed by CT imaging if CT was used at prior imaging). 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.

7.1.2.6.2 Tumor Imaging During the Trial

The imaging assessment should be performed at Week 6 (42 ± 7 days), Week 12 (84 ± 7 days), and Week 18 (126 ± 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 45 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 the local site investigator elects to continue treatment and follow irRECIST), the start of new anticancer therapy, withdrawal of consent, or death, whichever is earlier. 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 (ie, 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 7.1.2.6.6), disease progression should be confirmed by the site at least 4 weeks after central verification of site-assessed first radiologic evidence of PD in clinically stable subjects. Subjects who have unconfirmed disease progression may continue on treatment at the discretion of the site investigator until progression is confirmed by the site provided they have met the conditions detailed in Section 7.1.2.6.6. 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. An exception is detailed in Section 7.1.2.6.6.

7.1.2.6.3 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 9 weeks in Year 1 or 12 weeks after Year 1) to monitor disease status until (1) the start of new anticancer therapy, (2) disease progression, (3) death, or (4) the end of the study, whichever is earlier, should be used.

7.1.2.6.4 Second Course (Retreatment) Tumor Imaging

A scan must be performed within 28 days prior to 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 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 7.1.2.6.6), 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 anticancer therapy, withdrawal of consent, death, or notification by the Sponsor, whichever is earlier. 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 isn't 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 anticancer therapy, (2) disease progression, (3) death, or (4) the end of the study, whichever is earlier.

7.1.2.6.5 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 (eg, discontinuation of study therapy). Initial tumor imaging showing site-assessed PD should be submitted to the central imaging vendor immediately. The site will be notified via email if the central imaging vendor verifies PD using RECIST 1.1. Figure 2 illustrates the imaging flow involving verification of PD for clinically stable subjects.

7.1.2.6.6 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 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 who 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 as verified by the central imaging vendor, it is at the discretion of the local site investigator whether to continue a subject on study treatment until repeat imaging is obtained (using irRECIST for subject management, see Table 5 and Figure 2). 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 ≥4 weeks later in order to confirm PD by irRECIST per site assessment. 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 PD
4) Absence of progressive tumor at critical anatomical sites (eg, cord compression) requiring urgent alternative medical intervention

Any subject deemed clinically unstable should be discontinued from trial treatment at 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).

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

- Target lesion sum of diameters is <20% or there is less than a 5-mm absolute increase compared to the 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 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, study treatment and tumor imaging may continue per study schedule.

PD is confirmed at repeat imaging if ANY of the following occur by irRECIST:

- Target lesion sum of diameters remains ≥20 % and there is at least a 5-mm absolute increase compared to the 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.

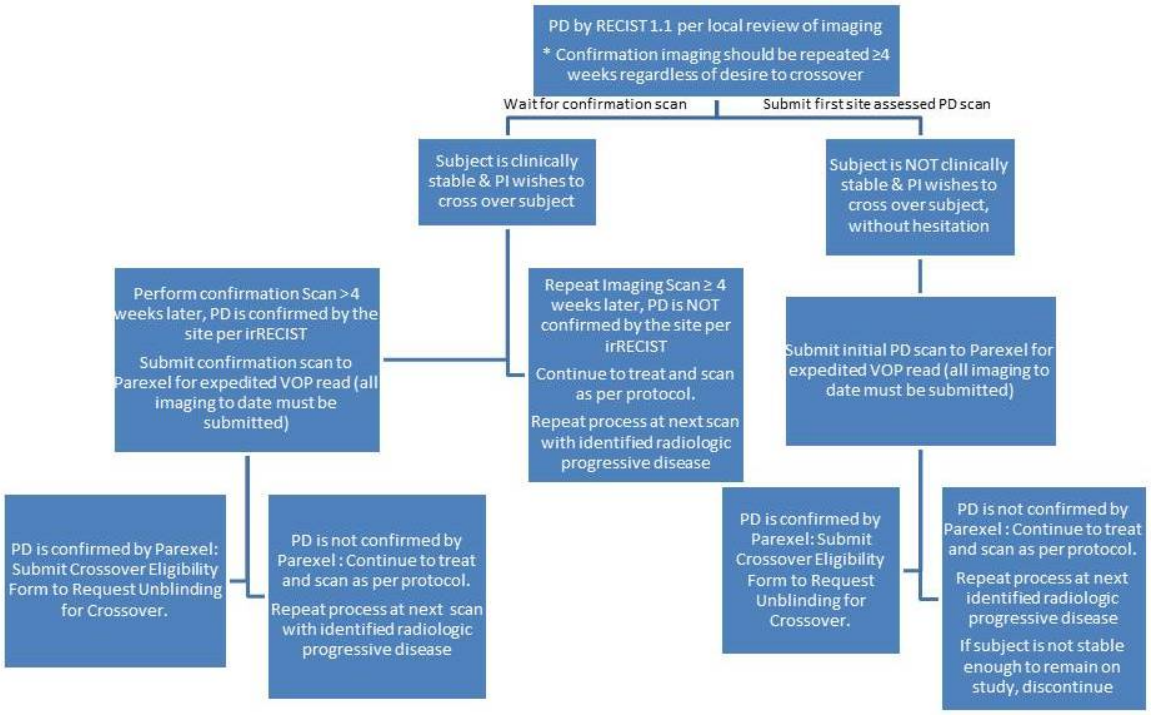
NOTE: If a subject has confirmed radiographic progression (ie, 2 scans at least 4 weeks apart demonstrating PD) per irRECIST, but the subject is achieving a clinically meaningful benefit, and there is no further increase in the tumor burden at the confirmatory tumor imaging, an exception to continue 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 outlined in Section 6.0 Trial Flow Chart and be submitted to the central imaging vendor.

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

Table 5 Imaging and Treatment after First Radiologic Evidence of PD

	Clinically Stable		Clinically Unstable	
	Imaging	**Treatment**	**Imaging**	**Treatment**
First radiologic evidence of PD by RECIST 1.1 which has been verified by the central imaging vendor	Repeat imaging at ≥4 weeks at site to confirm PD	May continue study treatment at the local site investigator's discretion while awaiting confirmatory tumor imaging by site by irRECIST	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	No additional imaging required	Discontinue treatment (exception is possible upon consultation with Sponsor)	No additional imaging required	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 imaging should occur according to the regular imaging schedule outlined in the protocol

Figure 2 Imaging and Treatment for Clinically Stable Subjects After First Radiologic Evidence of PD Assessed by the Site



7.1.2.7 Tumor Tissue Collection: PD-L1 Status

Participation in this trial will be dependent upon supplying tumor tissue for PD-L1 testing 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. Subjects whose submitted tissue is non-evaluable for PD-L1 status can still be eligible to participate in the study.

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 and study subjects. Analyses by PD-L1 biomarker status will be limited and documented.

If the subject (or their legally acceptable representative) provides documented informed consent for FBR, any leftover samples that would ordinarily be discarded at the end of the main study will be retained for FBR.

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 Procedure Manual.

7.1.3.1 Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

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

Table 6 Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Blood	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		
	Phosphorus		
	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.

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 the normal range.

7.1.3.2 Pharmacokinetic/Pharmacodynamic Evaluations

Pembrolizumab

The accumulation of robust PK and ADA data has allowed for the adequate characterization of the clinical pharmacology of pembrolizumab across indications. Therefore, the collection of PK and ADA samples for pembrolizumab are being discontinued. Blood samples for PK and ADA that have already been collected may be stored. Analysis will be performed only if required.

Exploratory drug-drug interaction analysis

The potential of drug interaction between biologics such as pembrolizumab and small molecule drugs is negligible. Therefore, collection of samples for the assessment of PK of paclitaxel and nab-paclitaxel is being discontinued. Blood samples for PK that have already been collected may be stored. Analysis will be performed only if required.

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, AE 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.

PROs (EQ-5D, EORTC QLQ-C30, and EORTC QLQ-LC13) are completed at Cycles 1 through 7 and then every third cycle (every 9 weeks) while on treatment up to 48 weeks. All PROs are also completed at the treatment discontinuation visit and the 30-day safety follow-up visit.

7.1.3.4 Blood for RNA Analyses and Biomarker Analyses (plasma, serum)

Blood for RNA analyses should be collected pre-dose on Day 1 of Cycles 1, 2, and 5, or at the time of discontinuation. Blood for biomarker analyses (plasma, serum) should be collected pre-dose on Day 1 of Cycles 1, 2, or at the time of discontinuation. Detailed instructions with specific time points per sample are provided in the Procedures Manual. Any leftover samples will be stored for FBR if the participant (or their legally acceptable representative) provides documented informed consent for FBR.

7.1.3.5 Planned Genetic Analysis Sample Collection

Sample collection, storage and shipment instructions for Planned Genetic Analysis samples will be provided in the Procedure Manual.

7.1.3.6 Future Biomedical Research Sample Collection

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

DNA for future research.

- Leftover RNA
- Leftover plasma and serum from biomarker analyses
- 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 7.1.5.5. 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

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

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

7.1.4.2 Blinding/Unblinding

When the investigator or sub-investigator needs to identify the drug 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. Subjects whose treatment assignment has been unblinded must be discontinued from study drug.

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.

In the event that unblinding has occurred, the circumstances around the unblinding (e.g., date, reason and person performing the unblinding) must be documented promptly, and the Sponsor Clinical Director notified as soon as possible. Only the principal investigator or delegate and the respective subject's code should be unblinded. Trial site personnel and Sponsor personnel directly associated with the conduct of the trial should not be unblinded. Subjects whose treatment assignment has been unblinded (by the investigator, Merck subsidiary, or through the emergency unblinding call center) must be discontinued from study drug.

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.

Documented informed consent must be obtained prior to performing any protocol-specific procedure. Results of a test performed prior to the subject providing documented informed 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 28 days prior to randomization.

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

7.1.5.2 Treatment Period Visit

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

7.1.5.3 Post-Trial

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 disease status. If the subject experienced a CR, PR, or SD during the Treatment Phase on pembrolizumab, and then experiences PD at any time during the 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 7.1.5.5. After the Second Course Phase, subjects should be followed for up to 2 years, with no option of retreatment with pembrolizumab on study.

Subjects who discontinue trial treatment for a reason other than disease progression will still be considered on-study and should continue with regularly scheduled assessments (also refer to Section 7.1.2.6.3), 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 is earlier. 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 is earlier. Subjects who are eligible per the requirements in Section 7.1.5.5 for treatment with pembrolizumab during the Second Course Phase may have up to 3 safety follow- up visits, after the Treatment Phase, after the Crossover Phase, and after the Second Course Phase.

7.1.5.3.2 Follow-up Visits

Follow-up visit requirements are outlined in Section 6.0 - Trial Flow Chart.

7.1.5.3.3 Survival Follow-up

Subjects who experience confirmed disease progression or start a new anticancer therapy, will move into 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 is earlier. 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 database locks, updated survival status may be requested during the course of the study by the Sponsor. For example, updated survival status may be requested prior to but not limited to an eDMC review, IA, and/or final analysis. 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

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

Subjects who were randomized to receive pembrolizumab or who crossed over to pembrolizumab from placebo may be eligible to receive pembrolizumab in the Second Course Phase of this study for up to 17 cycles if the subject:

- Stopped their initial treatment with pembrolizumab/placebo after attaining a confirmed CR by central review, were treated for at least 8 cycles with pembrolizumab/placebo, 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 pembrolizumab treatment after 35 treatments for reasons other than disease progression or intolerability.

AND

- Experienced an investigator-determined confirmed radiographic disease progression according to irRECIST after stopping their initial treatment with pembrolizumab due to achievement of a confirmed CR.
- Did not receive any other systemic anticancer therapy since the last dose of pembrolizumab. (Local treatment such as radiation or surgery as anticancer therapy is allowed; Sponsor consultation must be obtained and subjects should have recovered completely from side effects of local procedures. In subjects with brain metastases, neurological stability must be documented before initiating pembrolizumab.)
- Continues to meet Inclusion Criteria 7, 8, and 9.
- Does not meet Exclusion Criteria 2, 3, 4, 6-8, 11, 13, 14, and/or 22.

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 Phase

Subjects who are unblinded after verification for PD by blinded independent central radiological review, will have the opportunity to receive pembrolizumab monotherapy in the crossover phase. Subjects who permanently discontinue chemotherapy due to an AE, withdraw consent, or for any reason other than progressive disease, will not be eligible for crossover. Subjects who are unblinded will be allowed to crossover after documented PD by blinded independent central radiological review. Crossover subjects must not initiate treatment with pembrolizumab 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 after documented progressive disease based on RECIST 1.1. verified by central imaging vendor review. 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:

- Documentation of PD by central imaging vendor assessment.
- AEs (except alopecia and peripheral neuropathy) 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 other systemic anticancer therapies other than the chemotherapy administered during the treatment phase.
- If required, completed palliative radiotherapy (30 Gy or less) ≥7 days before the first dose of crossover trial treatment.

- Subject has adequate organ function as indicated by the laboratory values in Section 5.1.2.

7.1.5.7 Crossover Assessments and Procedures

Crossover subjects must not initiate treatment with pembrolizumab 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 the Crossover Flow Chart in Section 6.3. Screening procedures need to be completed within 28 days of confirmed PD (or up to 42 days from last dose if recovering from an 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 imaging used to determine PD can be used as the new baseline imaging for the Crossover Phase if 1) it occurred 30 days prior to receiving the first dose of pembrolizumab monotherapy and 2) no study treatment was received between the imaging and the 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 Section 7.1.5.5.

7.2 Assessing and Recording Adverse Events

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

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

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

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

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

All adverse events that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but

not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure. From the time of treatment allocation/randomization through 30 days following cessation of treatment, all adverse events must be reported by the investigator. Such events will be recorded at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in section 7.2.3.1. The investigator will make every attempt to follow all subjects with non-serious adverse events for outcome.

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

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

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

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 infant exposure during breastfeeding are not considered AEs, any pregnancy or infant exposure during breastfeeding in a participant (spontaneously reported to the investigator or their designee), including the pregnancy of a male participant's female partner, that occurs during the study are reportable to the Sponsor.

All reported pregnancies must be followed to the completion/termination of the pregnancy.

Any pregnancy complication will be reported as an AE or SAE.

The medical reason (example: maternal health or fetal disease) for an elective termination of a pregnancy will be reported as an AE or SAE. Prenatal testing showing fetus will be born with severe abnormalities/congenital anomalies that leads to an elective termination of a pregnancy will be reported as an SAE for the fetus.

Pregnancy outcomes of ectopic pregnancy, 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.

7.2.3 Immediate Reporting of Adverse Events to the Sponsor

7.2.3.1 Serious Adverse Events

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

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

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

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

Refer to Table 7 for additional details regarding each of the above criteria.

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

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

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

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

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

7.2.3.2 Events of Clinical Interest

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

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

For the time period beginning at treatment allocation/randomization through 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 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 an SAE within 24 hours of determination that the event is not progression of the cancer under study.

7.2.4 Evaluating Adverse Events

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

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

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

Table 7 Evaluating Adverse Events

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

V4.0 CTCAE Grading	**Grade 1**	**Mild; asymptomatic or mid symptoms; clinical or diagnostic observations only; intervention not indicated.**
	Grade 2	**Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.**
	Grade 3	**Severe or medically significant but not immediately life-threatening; hospitalization or prolongation or hospitalization indicated; disabling; limiting self-care ADL.**
	Grade 4	**Life threatening consequences; urgent intervention indicated.**
	Grade 5	**Death related to AE**
Seriousness	A serious adverse event is any adverse event occurring at any dose or during any use of Sponsor's product that:	
	†**Results in death**; or	
	†**Is life threatening; or** places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred (Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.); or	
	†**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or	
	†**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization 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 their best clinical judgment, including consideration of the above elements.		
Record one of the following	**Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Sponsor's product relationship).**	
Yes, there is a reasonable possibility of Sponsor's product relationship.	There is evidence of exposure to the Sponsor's product. The temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable. The AE is more likely explained by the Sponsor's product than by another cause.	
No, there is not a reasonable possibility of Sponsor's product relationship	Subject did not receive the Sponsor's product OR temporal sequence of the AE onset relative to administration of the Sponsor's product is not reasonable OR the AE is more likely explained by another cause than the Sponsor's product. (Also entered for a subject with overdose without an associated AE.)	

7.2.5 Sponsor Responsibility for Reporting Adverse Events

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

7.3 TRIAL GOVERNANCE AND OVERSIGHT

7.3.1 Scientific Advisory Committee

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

7.3.2 Executive Oversight Committee

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

7.3.3 Data Monitoring Committee

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

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

Specific details regarding composition, responsibilities, and governance, including the roles and responsibilities of the various members and the Sponsor protocol team; meeting facilitation; the trial governance structure; and requirements for and proper documentation of DMC reports, minutes, and recommendations will be described in 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 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 Collaboration agreement.

8.0 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, changes are made to primary and/or key secondary hypotheses, or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with ICH Guideline E-9). Changes to exploratory or other non-confirmatory analyses made after the protocol has been finalized, but prior to the conduct of any analysis, will be documented in a sSAP as needed and referenced in the CSR for the study. Separate analysis plans (ie, separate documents from the sSAP) may be developed for PK/modeling analysis, biomarker analysis, and genetic data analysis. Post hoc exploratory analyses will be clearly identified in the CSR.

8.1 Statistical Analysis Plan Summary

Key elements of the SAP are summarized below; the comprehensive plan is provided in Sections 8.2 through 8.11.

Study Design Overview	A Phase III Study of Carboplatin-Paclitaxel/Nab-Paclitaxel Chemotherapy with or without Pembrolizumab (MK-3475) in First Line Metastatic Squamous Non-small Cell Lung Cancer Subjects (KEYNOTE-407)
Treatment Assignment	Subjects will be randomized in a 1:1 ratio to receive pembrolizumab or saline placebo in combination with carboplatin and a taxane (investigators choice of paclitaxel or nab-paclitaxel). 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)
Dual Primary Endpoints/Hypotheses	1) PFS per RECIST 1.1 assessed by a blinded independent central imaging vendor 2) OS
Statistical Methods for Key Efficacy Analyses	The dual primary hypotheses on PFS and OS will be evaluated by comparing pembrolizumab to saline placebo in combination with carboplatin and a taxane 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. The stratified Miettinen and Nurminen method with sample size weights will be used for analysis of ORR.
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% CIs 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 the first dose of pembrolizumab.

Interim Analyses	There are 4 analyses planned for this study: 3 IAs and one final analysis. Results from the first 3 IAs will be reviewed by an eDMC. Details are provided in Section 8.7. • IA1 o Timing: To be performed after ~200 subjects have ~28 weeks of follow-up o Purpose: To demonstrate superiority of pembrolizumab in combination with carboplatin and a taxane in ORR • IA2 o Timing: To be performed after a target number of PFS events (~332) is observed o Purpose: 1) To demonstrate superiority of pembrolizumab in combination with carboplatin and a taxane in PFS; 2) To demonstrate superiority of pembrolizumab in combination with carboplatin and a taxane in OS • IA3 o Timing: To be performed after a target number of PFS events (~415) is observed o Purpose: 1) To demonstrate superiority of pembrolizumab in combination with carboplatin and a taxane in PFS; 2) To demonstrate superiority of pembrolizumab in combination with carboplatin and a taxane in OS Because of positive interim results for both PFS and OS, subsequent analyses will be conducted and reviewed by the Sponsor and may be performed at the planned time of final analysis, or as needed.
Multiplicity	The study uses the graphical method of Maurer and Bretz [42] to control multiplicity for multiple hypotheses as well as IAs. According to this approach, study hypotheses may be tested more than once, and when a particular null hypothesis is rejected, the alpha allocated to that hypothesis can be reallocated to other hypothesis tests. The overall type I error is controlled at 0.025 (one-sided) for the hypothesis testing of ORR, PFS, and OS. The pre-allocated alpha is 0.005, 0.01, and 0.01 for ORR, PFS, and OS, respectively. ORR may be tested at 0.005 or at 0.025 (if both PFS and OS are positive, using the p-value from IA1). PFS may be tested at 0.01 or at 0.015 (if ORR is positive but OS is not positive), or at 0.02 (if OS is positive but ORR is not positive) or at 0.025 (if both OS and ORR are positive). OS may be tested at 0.01 or at 0.02 (if PFS is positive but ORR is not positive) or 0.025 (if both PFS and ORR are positive). A Lan-DeMets O'Brien-Fleming approximation spending function will be used for the calculation of efficacy bounds for PFS and OS.
Sample Size and Power	The final analysis occurs after ~361 deaths are observed unless the trial is terminated early. With 361 deaths, the study has 92% power for detecting an HR of 0.7 at 0.025 (one-sided), ~90% power for detecting an HR of 0.7 at 0.02 (one-sided), and ~85% power for detecting an HR of 0.7 at 0.01 (one-sided). The planned sample size is approximately 560 subjects assuming ~15.5 months of enrollment.

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.

An eDMC will be convened to review accumulating safety data 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 IAs. The eDMC responsibilities and review schedules will be outlined in the eDMC charter. The recommendation of the eDMC will be communicated to an EOC of the Sponsor. In the event of a recommendation to halt the trial early due to safety concerns, the Sponsor will communicate this to the appropriate regulatory agencies. If the eDMC recommends modifications to the design of the protocol or discontinuation of the study, the EOC may be unblinded to results at the treatment level in order to act on these recommendations.

A limited number 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 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.

Positive interim results for both PFS and OS were observed. Thus, a limited number of Sponsor personnel have been unblinded to support regulatory filing. The extent to which individuals were unblinded to the results has been documented.

See Appendix 12.7 for country-specific information.

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

Dual Primary

PFS – RECIST 1.1 assessed by a blinded independent central imaging vendor

PFS is defined as the time from randomization to the first documented disease progression per RECIST 1.1 based on blinded independent central imaging vendor review or death due to any cause, whichever is earlier. See Section 8.6.1 for the censoring rules.

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 the last known contact.

Secondary

ORR – RECIST 1.1 assessed by a blinded independent central imaging vendor

ORR is defined as the proportion of subjects who have a CR or a PR. Responses are based on confirmed assessments by the blinded independent central imaging vendor review per RECIST 1.1.

DOR – RECIST 1.1 assessed by a blinded independent central imaging vendor

For subjects who demonstrated CR or PR, DOR is defined as the time from the first documented evidence of CR or PR until disease progression or death. Response duration for subjects who have not progressed or died at the time of analysis will be censored at the date of their last tumor assessment. Response duration will be calculated using RECIST 1.1 based on blinded independent radiologist review.

8.4.2 Safety Endpoints

Safety measurements are described in Section 4.2.3.4.

8.5 Analysis Populations

8.5.1 Efficacy Analysis Populations

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

See Appendix 12.7 for country-specific information.

8.5.2 Safety Analysis Populations

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

At least 1 laboratory or vital sign measurement obtained subsequent to at least 1 dose of study treatment is required for inclusion in the analysis of each specific parameter. To assess change from baseline, a baseline measurement is also required.

Extension Study

Chinese subjects randomized and treated in the extension study will not be included in the above primary safety analysis population. The Chinese ASaT population 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, HR) between the treatment arms. The HR and its 95% CI 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 a blinded independent central imaging vendor, 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 a blinded independent central imaging vendor, we will perform 2 sensitivity analyses with a different set of censoring rules. The first sensitivity analysis is the same as the primary analysis except that it censors at the last disease assessment without PD when PD or death is documented after more than 1 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 therapy subsequent to discontinuation of study-specified treatments, whichever is 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 8. 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 8 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 therapy 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 therapy is initiated	Censored at last disease assessment before new anticancer therapy	Censored at last disease assessment before new anticancer therapy	Progressed at date of new anticancer therapy
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, supportive analyses using the Restricted Mean Survival Time 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 subsequent disease progression after initiation of new anticancer therapy, or death from any cause, whichever is earlier, may be carried out. Patients alive and for whom a disease progression following initiation of new anticancer therapy has not been observed will be censored at the last time the subject was known to be alive and without 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 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, HR). The HR and its 95% CI 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. The Restricted Mean Survival Time method may be conducted for OS to account for the possible non-proportional hazards effect and to estimate the absolute benefit of experimental treatment. A cure-rate model may be applied to estimate the long-term effect.

Since subjects in the control arm are allowed to switch to pembrolizumab monotherapy after progressive disease, adjustment for the effect of crossover on OS may be performed based on

recognized methods, eg, a 2-stage method or the Rank Preserving Structural Failure Time model, 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)

The stratified Miettinen and Nurminen method will be used for the comparison of ORR between the 2 treatment groups. The difference in ORR and its 95% CI from the stratified Miettinen and Nurminen method with strata weighting by sample size 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, DOR will be summarized descriptively using Kaplan-Meier medians and quartiles. Only the subset of subjects who show a CR or PR will be included in this analysis.

8.6.1.4 Analysis Strategy for Key Efficacy Endpoints

Table 9 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 IAs is described in Section 8.7 - Interim Analyses and in Section 8.8 - Multiplicity.

Table 9 Analysis Strategy for Key Efficacy Endpoints

Endpoint/Variable (Description, Time Point)	Statistical Method†	Analysis Population	Missing Data Approach
Dual Primary Endpoints			
PFS per RECIST 1.1 by blinded independent 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 the last date the subject was known to be alive)
Key Secondary Endpoints			
ORR per RECIST 1.1 by blinded independent central imaging vendor	Test and Estimation: Stratified Miettinen and Nurminen method with sample size weights††	ITT	Subjects without assessments are considered non-responders and conservatively included in the denominator
DOR per RECIST 1.1 by blinded independent central imaging vendor	Descriptive statistics for range and Kaplan-Meier estimate of median	Patients in ITT population with an objective response	

† 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.

8.6.2 Statistical Methods for Safety Analyses

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

Adverse Events

AEs will be coded using the standard MedDRA and grouped by system organ class. AEs will be graded by the investigator according to the CTCAE, version 4.0.

Tiered Approach

The analysis of safety results will follow a tiered approach (Table 10). 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% CIs 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% CIs 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 events observed. Membership in Tier 2 requires that at least 4 subjects in any treatment group exhibit the event; all other adverse experiences and predefined limits of change will belong to Tier 3.

The threshold of at least 4 events was chosen because the 95% CI 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% CIs may be provided without adjustment for multiplicity, the CIs 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 values and vital signs, which 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 that is both drug-related and Grade 3-5, any AE which is both serious and drug-related, a dose modification due to AE, a discontinuation due to an AE, and death will be considered Tier 2 endpoints. The 95% CIs (Tier 2) will be provided for between- treatment differences in the percentage of subjects with events; these analyses will be performed using the unstratified Miettinen and Nurminen method (1985), an unconditional, asymptotic method.

Table 10 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 Analyses

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

There are 3 planned IAs in addition to the final analysis for this study. Details on the boundaries for establishing statistical significance with regard to efficacy are discussed further in Section 8.8. The trial will continue until the number of deaths (see Section 8.9) is approximately equal to the targeted number for the final analysis irrespective of the outcome from the IAs.

The analyses planned, endpoints evaluated, and drivers of timing are summarized in Table 11.

Table 11 Summary of Interim and Final Analyses Strategy

Analyses	Key Endpoints	Timing	Estimated Time after First Participant Randomized	Primary Purpose of Analysis
IA1	ORR	~ 200 subjects are followed for ~ 28 weeks so that each patient has at least 4 tumor assessments	~ 15 months	• Demonstrate ORR superiority
IA2	PFS OS	~ 332 PFS events have been observed	~ 20 months	• Demonstrate PFS superiority • Demonstrate OS superiority
IA3	PFS OS	~ 415 PFS events have been observed	~ 25 months	• Demonstrate PFS superiority • Demonstrate OS superiority
Final Analysis	OS	~ 361 deaths have occurred	~ 31 months	• Demonstrate OS superiority

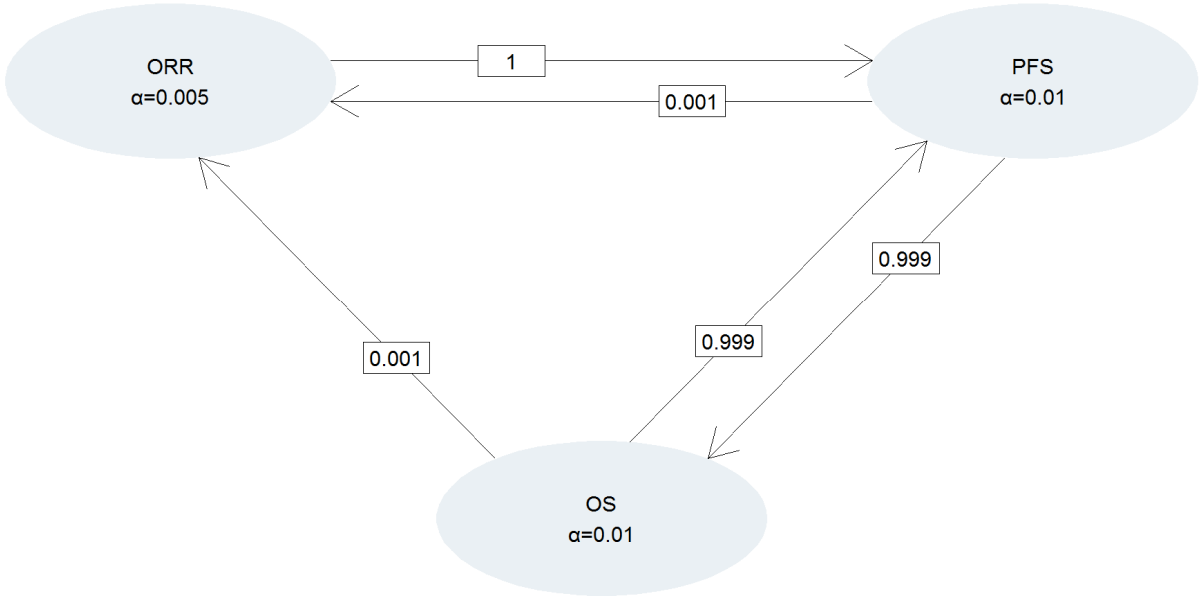
Because of positive results in the China extension for both PFS and OS observed at the IA, subsequent analyses may be performed at the planned time of final analysis, or as needed.

8.8 Multiplicity

The study uses the graphical method of Maurer and Bretz [42] to control multiplicity for multiple hypotheses as well as IAs. According to this approach, study hypotheses may be tested more than once, and when a particular null hypothesis is rejected, the alpha allocated to that hypothesis can be reallocated to other hypothesis tests. Figure 3 shows the initial one-sided alpha 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.

Figure 3 Type I Error Reallocation Strategy Following Closed Testing Principle



ORR=objective response rate; OS=overall survival; PFS=progression-free survival.
Note: If both PFS and OS null hypotheses are rejected, the reallocation strategy allows re-testing of ORR at alpha=0.025 based on the p-value at IA1.

8.8.1 Objective Response Rate

The study allocates alpha=0.005, one-sided, to test ORR, and ORR is tested only at IA1. However, if the test does not reach statistical significance at IA1, the p-value from IA1 can be compared to an updated alpha-level if the null hypotheses for both PFS and OS are rejected at a later time. Power at the possible alpha-levels as well as the approximate treatment difference required to reach the bound (ORR difference) are shown in Table 12, assuming underlying 25% and 50% response rates in the control and experimental groups, respectively.

Table 12 Possible Alpha-levels and Approximate ORR Difference Required to Demonstrate Efficacy for ORR at IA1

Alpha	ORR difference	Power
0.005	~ 0.18	0.84
0.025	~ 0.13	0.94

8.8.2 Progression-free Survival

The initial alpha-level for testing PFS is 0.01. If the null hypothesis for ORR is rejected, Table 12 shows that its alpha=0.005 is fully reallocated to PFS hypothesis testing. If the null hypothesis for OS is rejected, then alpha=0.01 is essentially fully reallocated to PFS hypothesis testing. Thus, the PFS null hypothesis may be tested at alpha=0.01, alpha=0.015 (if the ORR null hypothesis is rejected but not the OS null hypothesis), alpha=0.02 (if the OS null hypothesis is rejected but not the ORR null hypothesis), or alpha=0.025 (if both the ORR and OS null hypotheses are rejected). Table 13 shows the boundary properties for each of these alpha-levels for the IAs, which were derived using a Lan-DeMets O'Brien-Fleming spending function. Note that the final row indicates the total power to reject the null hypothesis for PFS at each alpha-level. If the actual number of events at the PFS analyses differ from those specified in the table, the bounds will be adjusted using the Lan-DeMets O'Brien-Fleming spending function accordingly. Also note that if the OS null hypothesis is rejected at an IA or final analysis, each PFS IA and final analysis test may be compared to its updated bounds considering the alpha reallocation from the OS hypothesis.

Table 13 Efficacy Boundaries and Properties for Progression-free Survival Analyses

Analysis	Value	α=0.01	α=0.015	α=0.02	α=0.025
IA2: 80%* N: 560 Events: 332 Month: 20	Z	-2.6539	-2.4817	-2.3536	-2.2504
	p (1-sided) [§]	0.004	0.0065	0.0093	0.0122
	HR at bound[%]	0.7473	0.7616	0.7723	0.7811
	P(Cross) if HR=1[†]	0.004	0.0065	0.0093	0.0122
	P(Cross) if HR=0.7[#]	0.7243	0.7787	0.8148	0.8411
IA3: 100%* N: 560 Events: 415 Month:25	Z	-2.3737	-2.2244	-2.1138	-2.025
	p (1-sided) [§]	0.0088	0.0131	0.0173	0.0214
	HR at bound[%]	0.7921	0.8038	0.8126	0.8197
	P(Cross) if HR=1[†]	0.01	0.015	0.02	0.025
	P(Cross) if HR=0.7[#]	0.9	0.9243	0.9392	0.9494

*Percentage of expected number of events at final analysis required at interim analysis.
[§]p (1-sided) is the nominal alpha for testing.
[%]HR at bound is the approximate HR required to reach an efficacy bound.
[†]P(Cross if HR=1) is the cumulative probability of crossing a bound under the null hypothesis.
[#]P(Cross if HR=0.7) is the cumulative probability of crossing a bound under the alternative hypothesis.

8.8.3 Overall Survival

The OS hypothesis may be tested at alpha=0.01 (initially allocated alpha), alpha=0.02 (if the PFS but not the ORR null hypothesis is rejected), or alpha=0.025 (if both the ORR and PFS null hypotheses are rejected). Table 14 demonstrates the bounds and boundary properties for OS hypothesis testing derived using a Lan-DeMets O'Brien-Fleming spending function. If the actual number of OS events at the IA and final analyses differs from those specified in the table, the bounds will be adjusted using the Lan-DeMets O'Brien-Fleming spending function accordingly.

Table 14 Efficacy Boundaries and Properties for Overall Survival Analyses

Analysis	Value	α=0.01	α=0.02	α=0.025
IA2: 59%* N: 560 Events: 212 Month: 20	Z	-3.1648	-2.8202	-2.702
	p (1-sided) §	0.0008	0.0024	0.0034
	HR at bound%	0.6474	0.6788	0.6899
	P(Cross) if HR=1†	0.0008	0.0024	0.0034
	P(Cross) if HR=0.7 #	0.2849	0.4115	0.458
IA3: 79%* N: 560 Events: 286 Month: 25	Z	-2.6914	-2.3992	-2.2995
	p (1-sided) §	0.0036	0.0082	0.0107
	HR at bound %	0.7274	0.7530	0.7619
	P(Cross) if HR=1†	0.0038	0.009	0.0117
	P(Cross) if HR=0.7#	0.6312	0.7362	0.7684
Final N: 560 Events: 361 Month: 31	Z	-2.3742	-2.116	-2.028
	p (1-sided) §	0.0088	0.0172	0.0213
	HR at bound %	0.7789	0.8003	0.8078
	P(Cross) if HR=1†	0.01	0.02	0.025
	P(Cross) if HR=0.7 #	0.85	0.9034	0.9181

*Percentage of expected number of events at final analysis required at interim analysis.
§p (1-sided) is the nominal α for testing.
%HR at bound is the approximate HR required to reach an efficacy bound.
†P(Cross if HR=1) is the cumulative probability of crossing a bound under the null hypothesis.
#P(Cross if HR=0.7) is the cumulative probability of crossing a bound under the alternative hypothesis.

8.9 Sample Size and Power Calculations

With ~200 subjects, the study has ~84% power for detecting a 25% difference in ORR (50% vs. 25%) or ~97% power for detecting a 30% difference in ORR (50% vs. 20%) at initially assigned 0.005 (one-sided) significance level. The study has ~94% power for detecting a 25% difference in ORR (50% vs. 25%) or ~99% power for detecting a 30% difference in ORR (50% vs. 20%) at 0.025 (one-sided) significance level.

With 415 PFS events, the study has ~90% power for detecting an HR of 0.7 at initially-assigned 0.01 (one-sided) significance level, ~92% power for detecting an HR of 0.7 at 0.015 (one-sided) significance level, ~94% power for detecting an HR of 0.7 at 0.02 (one-sided) significance level, and ~95% power for detecting an HR of 0.7 at 0.025 (one-sided) significance level.

With 361 deaths, the study has ~85% power for detecting an HR of 0.7 at 0.01 (one-sided) significance level, ~90% power for detecting an HR of 0.7 at 0.02 (one-sided) significance level, and ~92% power for detecting an HR of 0.7 at 0.025 (one-sided) significance level.

The planned sample size is approximately 560 subjects assuming: (1) the enrollment period is 15.5 months and the ramp-up period of enrollment is 7 months; (2) median PFS is 6 months in the control group and the true HR is 0.7; (3) median OS is 12 months in the control

group and the true HR is 0.7; (4) the annual dropout rate is 3% for PFS and 1% for OS; (5) the number of events and alpha levels of IAs and final analysis are as specified in Section 8.7 and Section 8.8.

See Appendix 12.7 for country-specific information.

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:

- Age category (<65, ≥65 years)
- ECOG Performance Scale (0, 1)
- Sex (female, male)
- Race (white, non-white)
- Geographic region of enrolling site (East Asia, non-East Asia)
- Smoking status (never, former/ current)
- Brain metastasis status at baseline (yes, no)
- PD-L1 expression (TPS <1%, 50%>TPS ≥1%, or TPS ≥50%)
- Taxane chemotherapy (paclitaxel, nab-paclitaxel)

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 15.

Clinical supplies will be packaged to support enrollment and replacement subjects as required. When a replacement subject is required, the Sponsor or designee needs to be contacted prior to dosing the replacement supplies.

Table 15 Product Descriptions

Product Name & Potency	Dosage Form	Source/Additional Information
Pembrolizumab (MK-3475) 100 mg / 4 mL	Solution for Infusion	Provided centrally by the Sponsor.
Nab-Paclitaxel 100mg vial	Powder for Infusion	Provided centrally by the Sponsor or locally by the trial site, subsidiary, or designee.
Carboplatin 10 mg/mL, 60 mL	Solution for Infusion	Provided centrally by the Sponsor or locally by the trial site, subsidiary, or designee.
Paclitaxel 6 mg/mL, 16.7 mL	Solution for Infusion	Provided centrally by the Sponsor or locally by the trial site, subsidiary, or designee.

All supplies indicated in Table 15 will be provided per the "Source/Additional Information" column depending on local country operational requirements.

Any commercially available product not included in Table 15 will be provided by the trial site, subsidiary or designee. Every attempt should be made to source these supplies from a single lot/batch number. The trial site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product as per local guidelines unless otherwise instructed by the Sponsor.

9.2 Packaging and Labeling Information

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

All supplies will be provided open label. Pembrolizumab will be provided as non-kitted single vials or as single/multi vials in a kit box. The 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/vaccine 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, reason and person performing the unblinding) must be documented promptly, and the Sponsor Clinical Director notified as soon as possible. Only the principal investigator or delegate and the respective subject's code should be unblinded. Trial site personnel and Sponsor personnel directly associated with the conduct of the trial should not be unblinded to treatment assignment. Subjects whose treatment assignment has been unblinded (by the investigator, Merck subsidiary, or through the emergency unblinding call center) must be discontinued from study drug.

Section 5.8 outlines the criteria for allowing subjects who are discontinued from treatment to continue to be monitored in the trial.

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 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.

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12.0 APPENDICES

12.1 Code of Conduct for Clinical Trials

Merck Sharp & Dohme LLC, Rahway, NJ, USA (MSD)
Code of Conduct for Interventional Clinical Trials

I. Introduction

A. Purpose

MSD, 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 participants in clinical trials is the overriding concern in the design and conduct of clinical trials. In all cases, MSD clinical trials will be conducted in compliance with local and/or national regulations (including all applicable data protection laws and regulations), and International Council for Harmonisation Good Clinical Practice (ICH-GCP), and also in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

Highest ethical and scientific standards shall be endorsed for all clinical interventional investigations sponsored by MSD 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 that are observational in nature, or which are retrospective. Further, this Code does not apply to investigator-initiated trials, which are not under the full control of MSD.

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 MSD or comparator products. Alternatively, MSD may conduct outcomes research trials, trials to assess or validate various endpoint measures, or trials to determine patient preferences, etc.

The design (i.e., participant population, duration, statistical power) must be adequate to address the specific purpose of the trial and shall respect the data protection rights of all participants, trial site staff and, where applicable, third parties. All trial protocols are and will be assessed for the need and capability to enroll underrepresented groups. Participants must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

MSD's clinical trials are conducted globally in many different countries and in diverse populations, including people of varying age, race, ethnicity, gender, and accounting for other potential disease related factors. MSD selects investigative sites based on medical expertise, access to appropriate participants, adequacy of facilities and staff, previous performance in clinical trials, as well as budgetary considerations. Prior to trial initiation, sites are evaluated by MSD personnel (or individuals acting on behalf of MSD) to assess the ability to successfully conduct the trial.

Where appropriate, and in accordance with regulatory authority guidance, MSD will make concerted efforts to raise awareness of clinical trial opportunities in various communities. MSD will seek to engage underrepresented groups and those disproportionately impacted by the disease under study. MSD will support clinical trial investigators to enroll underrepresented groups and expand access to those who will ultimately use the products under investigation.

3. Site Monitoring/Scientific Integrity

Investigative trial sites are monitored to assess compliance with the trial protocol and Good Clinical Practice (GCP). MSD reviews clinical data for accuracy, completeness, and consistency. Data are verified versus source documentation according to standard operating procedures. Per MSD policies and procedures, if potential fraud, scientific/research misconduct, privacy incidents/breaches or Clinical Trial-related Significant Quality Issues are reported, such matters are investigated. When necessary, appropriate corrective and/or preventative actions are defined and regulatory authorities and/or ethics review committees are notified.

B. Publication and Authorship

Regardless of trial outcome, MSD commits to publish the primary and secondary results of its registered trials of marketed products in which treatment is assigned, according to the pre-specified plans for data analysis. To the extent scientifically appropriate, MSD seeks to publish the results of other analyses it conducts that are important to patients, physicians, and payers. 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 such as multiplicity.

MSD's policy on authorship is consistent with the recommendations published by the International Committee of Medical Journal Editors (ICMJE). 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. MSD funding of a trial will be acknowledged in publications.

III. Participant Protection

A. Regulatory Authority and Ethics Committee Review (Institutional Review Board [IRB]/Independent Ethics Committee [IEC])

All protocols and protocol amendments will be submitted by MSD for regulatory authority acceptance/authorization prior to implementation of the trial or amendment, in compliance with local and/or national regulations.

The protocol, protocol amendment(s), informed consent form, investigator's brochure, and other relevant trial documents must be reviewed and approved by an IRB/IEC before being implemented at each site, in compliance with local and/or national regulations. Changes to the protocol that are required urgently to eliminate an immediate hazard and to protect participant safety may be enacted in anticipation of ethics committee approval. MSD will inform regulatory authorities of such new measures to protect participant safety, in compliance with local and/or national regulations.

B. Safety

The guiding principle in decision-making in clinical trials is that participant welfare is of primary importance. Potential participants 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.

All participation in MSD clinical trials is voluntary. Participants enter the trial only after informed consent is obtained. Participants may withdraw from an MSD 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

MSD is committed to safeguarding participant confidentiality, to the greatest extent possible, as well as all applicable data protection rights. Unless required by law, only the investigator, Sponsor (or individuals acting on behalf of MSD), ethics committee, and/or regulatory authorities will have access to confidential medical records that might identify the participant by name.

D. Genomic Research

Genomic research will only be conducted in accordance with a protocol and informed consent authorized by an ethics committee.

IV. Financial Considerations

A. Payments to Investigators

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

MSD does not pay for participant referrals. However, MSD may compensate referring physicians for time spent on chart review and medical evaluation to identify potentially eligible participants.

B. Clinical Research Funding

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

V. Investigator Commitment

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

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[3,4]

The specimens consented and/or collected in this study as outlined in Section 7.1.3.6 will be used in various experiments to understand:

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

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

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

3. Summary of Procedures for Future Biomedical Research[3,4]

a. Participants for Enrollment

All participants enrolled in the clinical study will be considered for enrollment in future biomedical research.

b. Informed Consent

Informed consent for specimens (ie, DNA, RNA, protein, etc.) will be obtained during screening for protocol enrollment from all participants or legal guardians, at a study visit by the investigator or his or her designate. Informed consent for future biomedical research should be presented to the participants on the visit designated in the SoA. If delayed, present consent at next possible Participant Visit. Consent

forms signed by the subject will be kept at the clinical trial site under secure storage for regulatory reasons.

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

c. eCRF Documentation for Future Biomedical Research Specimens

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

d. Future Biomedical Research Specimen Collections

Collection of specimens for future biomedical research will be performed as outlined in the SoA. In general, if additional blood specimens are being collected for future biomedical research, these will usually be obtained at a time when the participant is having blood drawn for other trial purposes.

4. Confidential Participant Information for Future Biomedical Research[3,4]

In order to optimize the research that can be conducted with future biomedical research specimens, it is critical to link participants' 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 participant characteristics like sex, age, medical history and treatment outcomes are critical to understanding clinical context of analytical results.

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

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

5. Biorepository Specimen Usage[3,4]

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

6. Withdrawal From Future Biomedical Research[3,4]

Participants may withdraw their consent for FBR and ask that their biospecimens not be used for FBR. Participants may withdraw consent at any time by contacting the study investigator. If medical records for the main trial are still available, the investigator will

contact the Sponsor using the designated mailbox (clinical.specimen.management@MSD.com). Subsequently, the participant's specimens will be flagged in the biorepository and restricted to study use only. If specimens were collected from study participants specifically for FBR, these specimens will be removed from the biorepository and be destroyed. Documentation will be sent to the investigator confirming withdrawal and/or destruction, if applicable. It is the responsibility of the investigator to inform the participant of completion the withdrawal and/or destruction, if applicable. Any analyses in progress at the time of request for withdrawal/destruction or already performed before the request being received by the Sponsor will continue to be used as part of the overall research study data and results. No new analyses would be generated after the request is received.

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

7. Retention of Specimens[3,4]

Future biomedical research specimens will be stored in the biorepository for potential analysis for up to 20 years from the end of the 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 study 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 study, the study 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[3,4]

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

9. Reporting of Future Biomedical Research Data to Participants[3,4]

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

If important research findings are discovered, the Sponsor may publish results, present results in national meetings, and make results accessible on a public website in order to

rapidly report this information to doctors and participants. Participants 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[3,4]

Every effort will be made to recruit all subjects diagnosed and treated on Sponsor clinical studies for future biomedical research.

11. Risks Versus Benefits of Future Biomedical Research[3,4]

For future biomedical research, risks to the participant have been minimized and are described in the future biomedical research informed consent.

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

12. Questions

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

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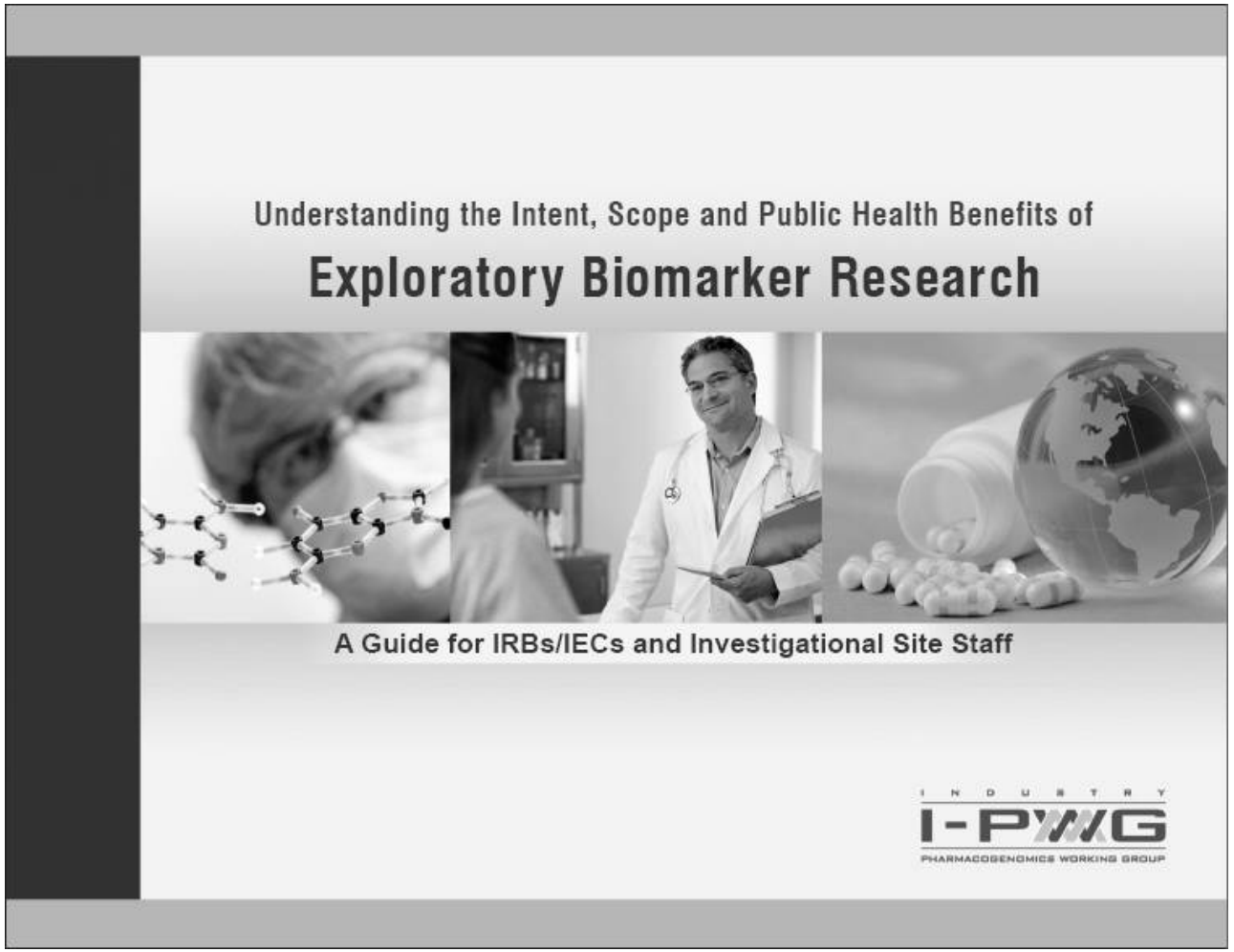
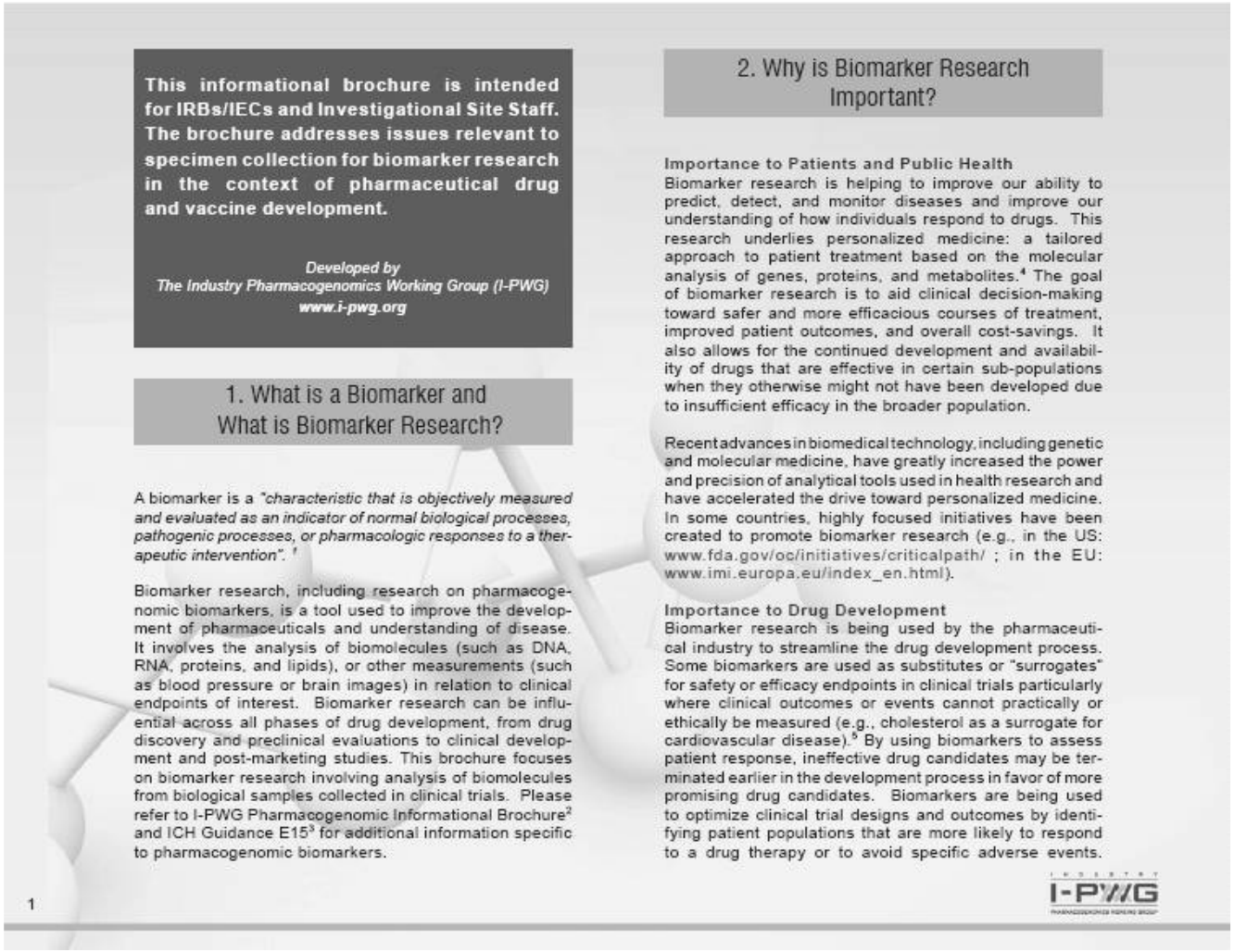
3. Industry Pharmacogenomics Working Group [Internet]: Understanding the Intent, Scope and Public Health Benefits of Exploratory Biomarker Research: A Guide for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/
4. Industry Pharmacogenomics Working Group [Internet]: Pharmacogenomics Informational Brochure for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/

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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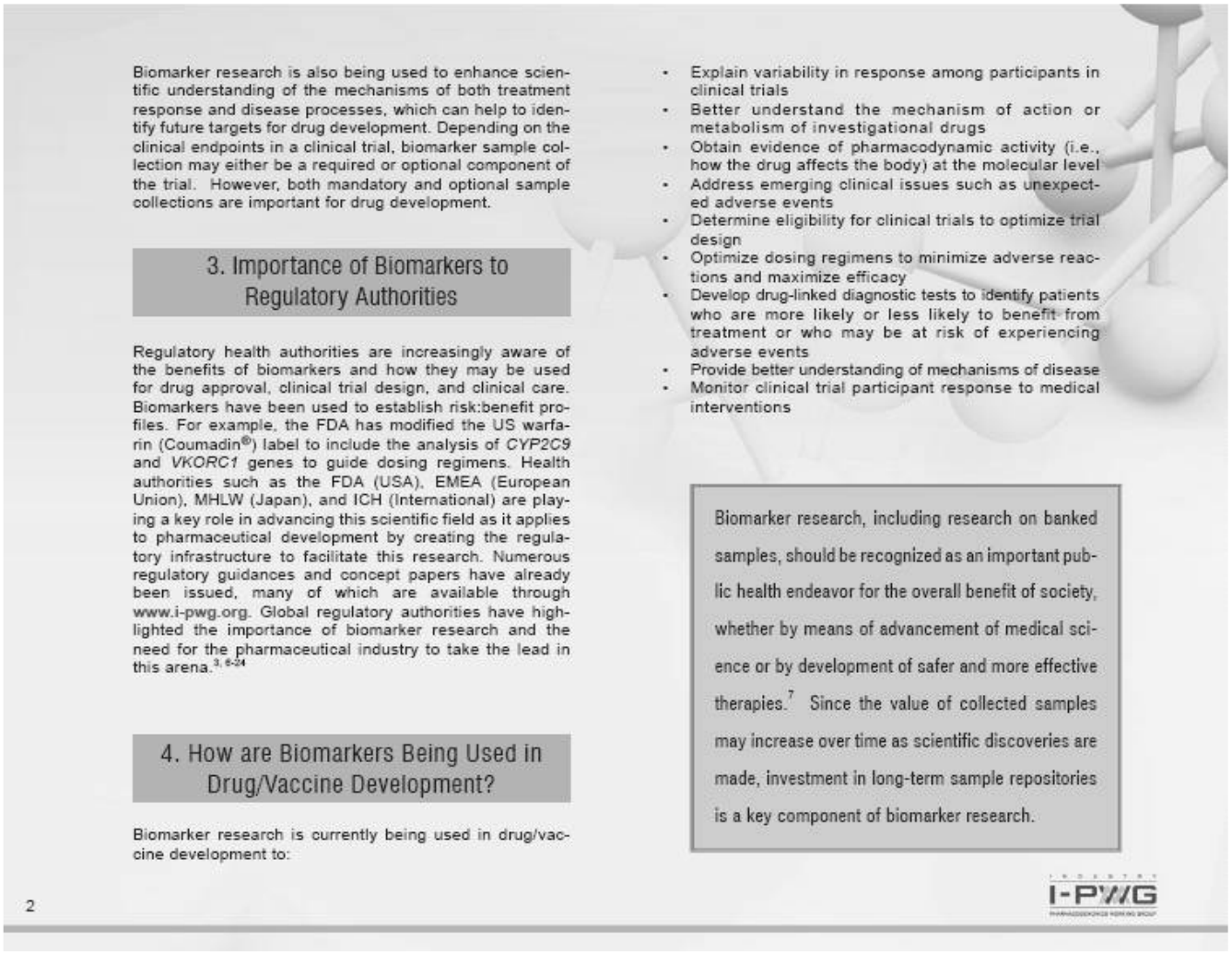

Biomarker research is also being used to enhance scientific understanding of the mechanisms of both treatment response and disease processes, which can help to identify future targets for drug development. Depending on the clinical endpoints in a clinical trial, biomarker sample collection may either 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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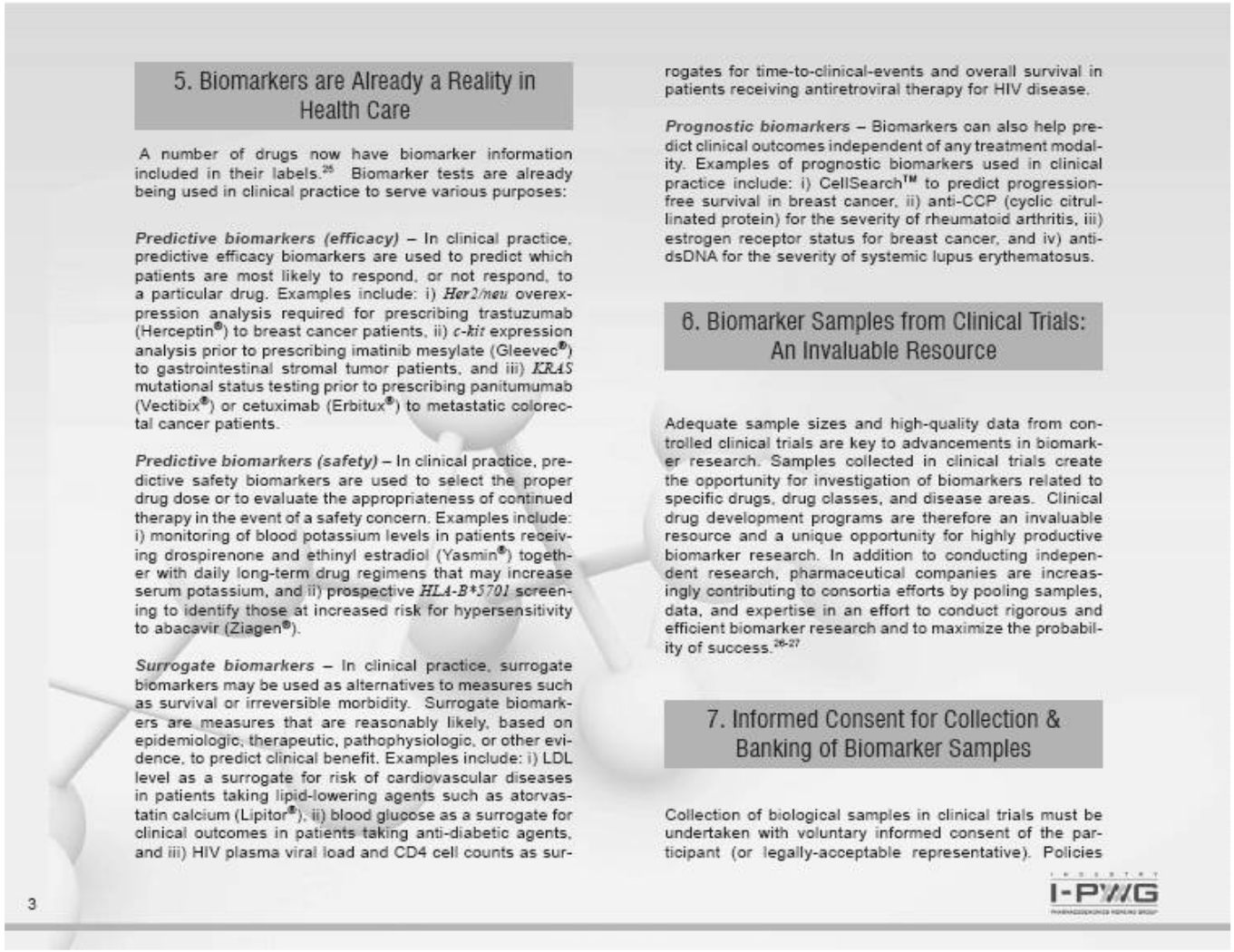

5. Biomarkers are Already a Reality in Health Care

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.[28-31]

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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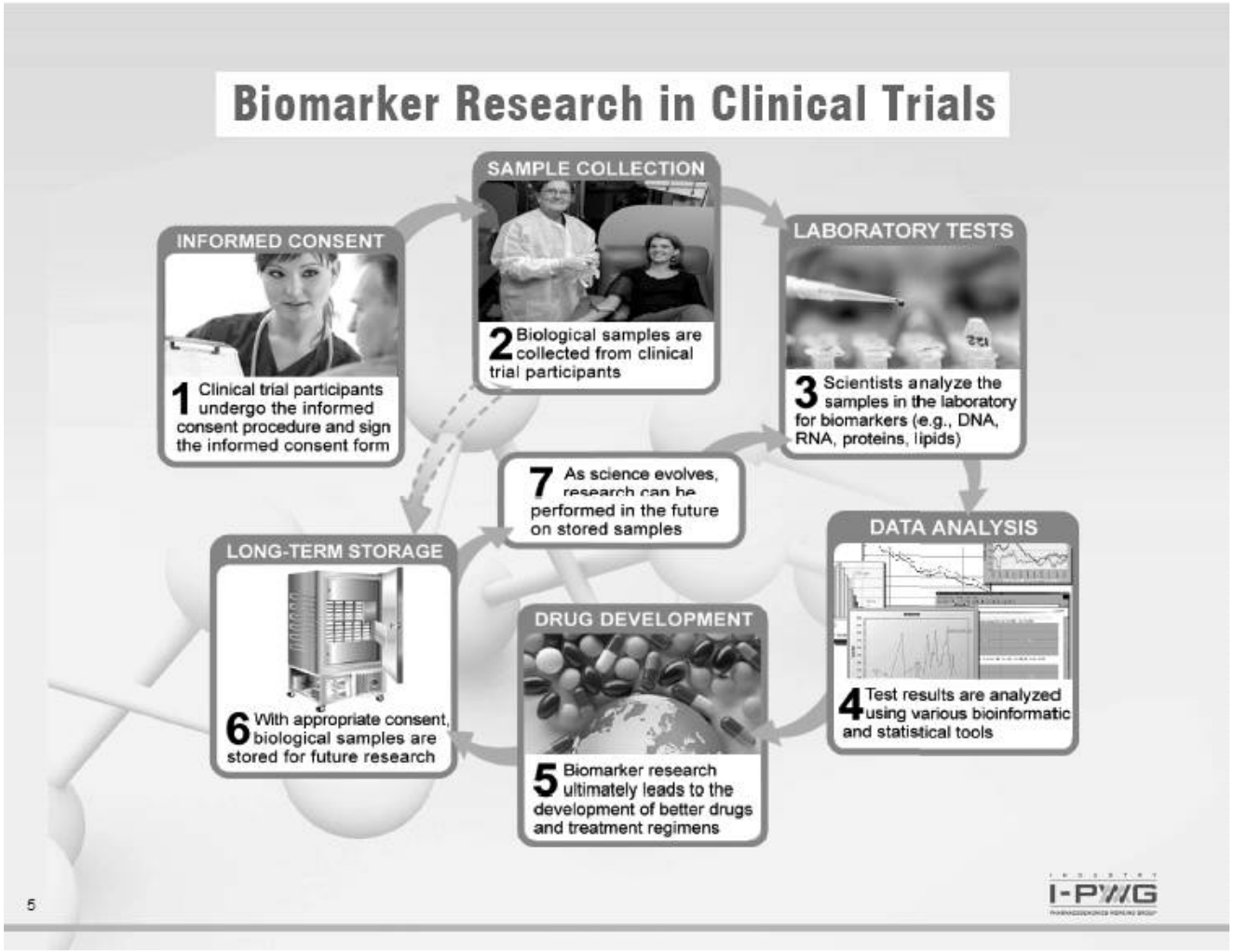
Biomarker Research in Clinical Trials
SAMPLE COLLECTION
2 Biological samples are collected from clinical trial participants
LABORATORY TESTS
3 Scientists analyze the samples in the laboratory for biomarkers (e.g., DNA, RNA, proteins, lipids)
INFORMED CONSENT
1 Clinical trial participants undergo the informed consent procedure and sign the informed consent form
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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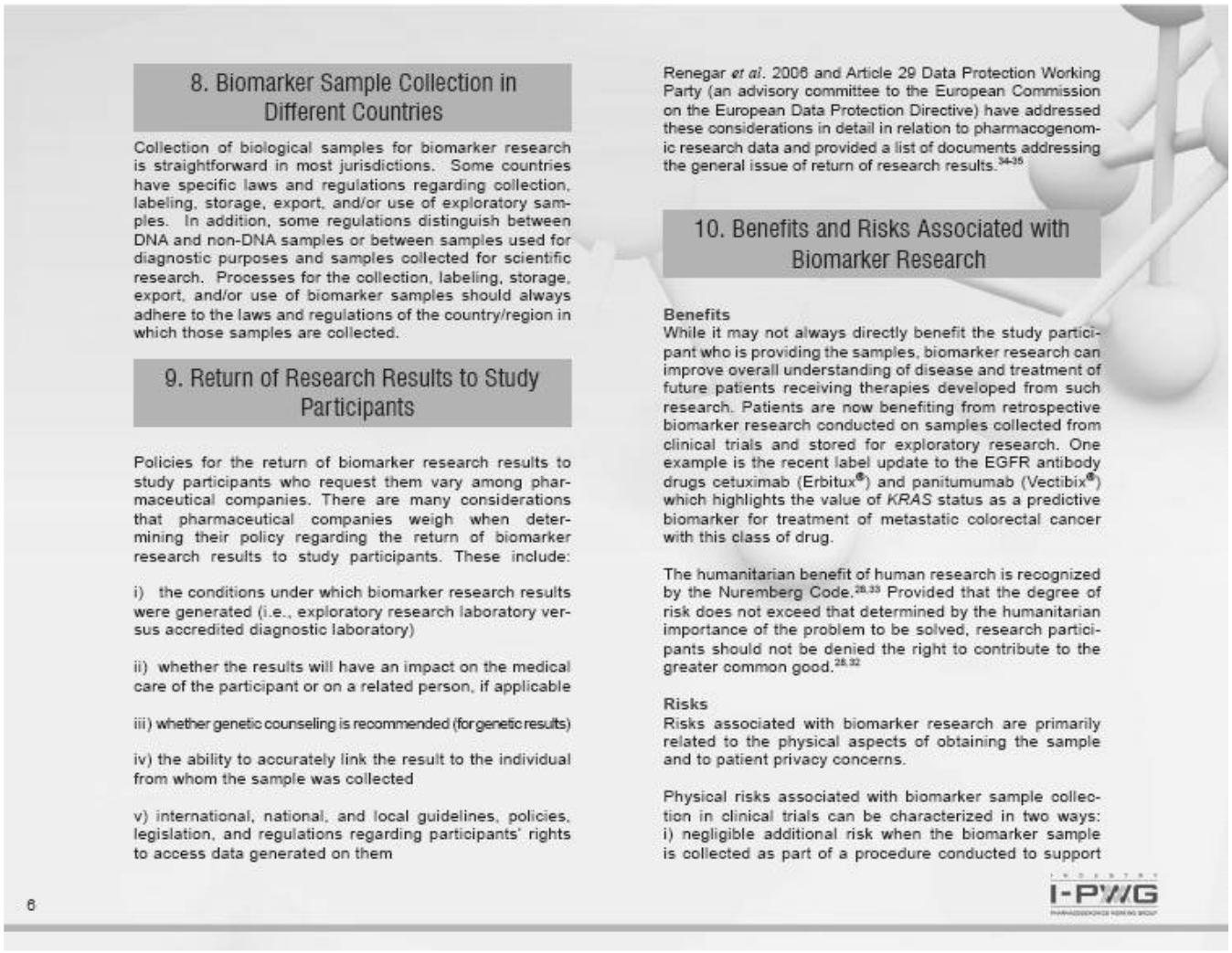

8. Biomarker Sample Collection in Different Countries

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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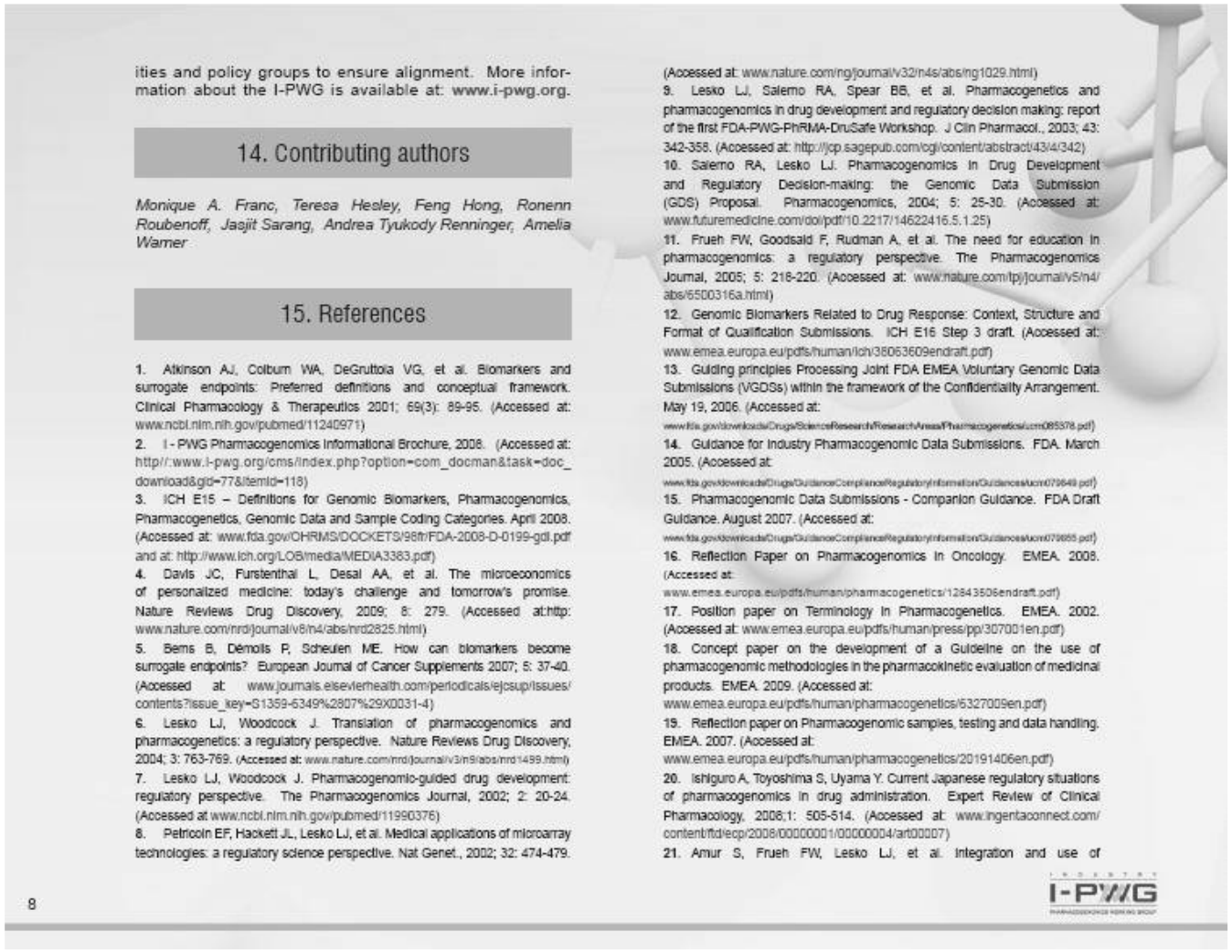

ities and policy groups to ensure alignment. More information about the I-PWG is available at: www.i-pwg.org.

14. Contributing authors

Monique A. Franc, Teresa Hesley, Feng Hong, Ronenn Roubenoff, Jasjit Sarang, Andrea Tyukody Renninger, Amelia Warner

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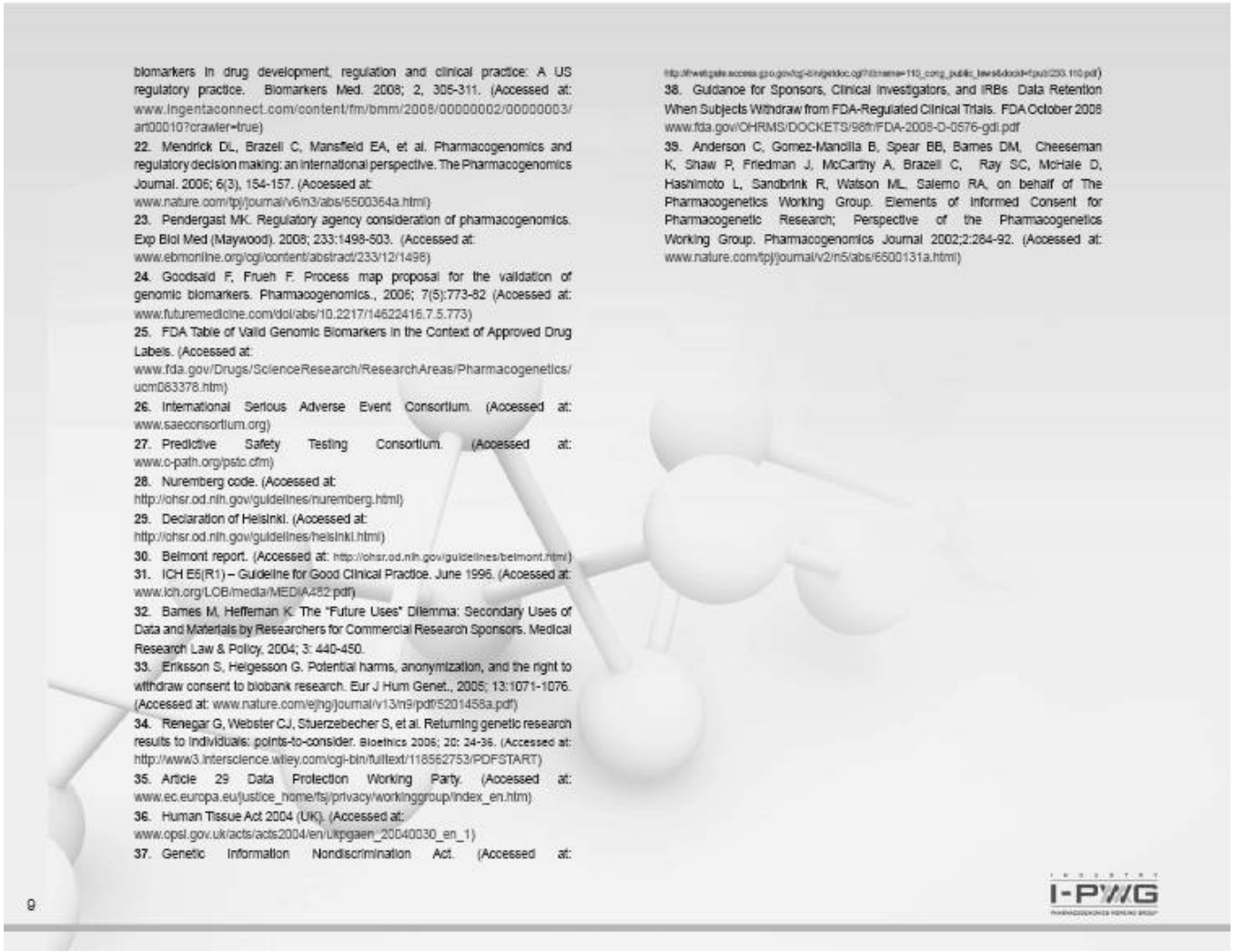

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12.4 List of Abbreviations

Abbreviation/Term	Definition
1L	first line
5-HT3	5-hydroxytryptamine 3
ADA	anti-drug antibodies
AE	adverse event
ALK	anaplastic lymphoma kinase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
ASaT	all-subjects-as-treated
AST	aspartate aminotransferase
AUC	area under the curve
β-HCG	beta human chorionic gonadotropin
BSC	best supportive care
CBC	complete blood count
CD	cluster of differentiation
CI	confidence interval
CNS	central nervous system
COPD	chronic obstructive pulmonary disease
CR	complete response
CrCl	calculated creatinine clearance
CRF	Case Report Form
CSF	colony-stimulating factor
CSR	Clinical Study Report
CT	computed tomography
CTCAE	Common Toxicity Criteria for Adverse Events
CTLA-4	cytotoxic T lymphocyte antigen-4
DLT	dose-limiting toxicity
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DOR	duration of response
ECG	electrocardiogram
ECI	event of clinical interest
ECOG	Eastern Cooperative Oncology Group
eDMC	external Data Monitoring Committee
EGFR	epidermal growth factor receptor
EMA	European Medicines Agency
EOC	Executive Oversight Committee
ERC	Ethics Review Committee
EU	European Union
FBR	Future Biomedical Research
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GFR	glomerular filtration rate
Hb	hemoglobin
HBV	hepatitis B
HCV	hepatitis C
HIV	human immunodeficiency virus
HR	hazard ratio
IA	interim analysis

Abbreviation/Term	Definition
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IFN	interferon
Ig	immunoglobulin
IHC	immunohistochemistry
IL	interleukin
INR	international normalized ratio
IO	immuno-oncology
irAE	immune-related adverse event
IRB	Institutional Review Board
irRECIST	immune-related Response Evaluation Criteria in Solid Tumors
ITT	intent-to-treat
IV	intravenous(ly)
IVD	in vitro diagnostics
IVRS	interactive voice response system
IWRS	interactive web response system
kg	kilogram
LDH	lactate dehydrogenase
mAb	monoclonal antibody
MASCC	Multinational Association of Supportive Care in Cancer
mcL	microliters
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
mg/kg	milligram per kilogram
MRI	magnetic resonance imaging
mRNA	messenger RNA
MSI	microsatellite instability
MTD	maximum tolerated dose
NA or N/A	not applicable
nab-paclitaxel	nano particle albumin-bound paclitaxel
NCI	National Cancer Institute
NSCLC	non-small cell lung cancer
ORR	overall response rate
OS	overall survival
OTC	over-the-counter
PD	progressive disease
PD-1	programmed cell death 1
PD-L1	programmed cell death ligand 1
PD-L2	programmed cell death ligand 2
PET	positron emission tomography
PFS	progression-free survival
PFS2	second progression-free survival
PK	pharmacokinetic(s)
PR	partial response
PRO	patient-reported outcome
PT	prothrombin time
RCC	renal cell carcinoma
RECIST 1.1	Response Evaluation Criteria in Solid Tumors, version 1.1
RNA	ribonucleic acid
RR	response rate

Abbreviation/Term	Definition
Q2W	once every 2 weeks
Q3W	once every 3 weeks
SAE	serious adverse event
SAP	Statistical Analysis Plan
sb-paclitaxel	solvent-based paclitaxel
SFU	survival follow-up
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SNP	single-nucleotide polymorphism
SOC	standard of care
sSAP	supplemental SAP
TIL	tumor-infiltrating lymphocyte
TMDD	target-mediated drug disposition
TNBC	triple-negative breast cancer
TPS	Tumor Proportion Score
Treg	regulatory T cell
TSH	thyroid stimulating hormone
TTP	time-to-progression
ULN	upper limit of normal
US	United States
WHO	World Health Organization

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

The descriptions and grading scales found in the revised NCI CTCAE, version 4.0 will be utilized for AE reporting. (http://ctep.cancer.gov/reporting/ctc.html).

12.6 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.

12.7 Country-specific Information: Extension Study in China

Section 2.1 Trial Design

After the enrollment period of the global study is completed, subjects from China will continue to be enrolled in the extension study, until the target number of 120 Chinese subjects is reached, to collect additional efficacy and safety data in Chinese subjects in order to support future local registration in China. 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 sSAP for Chinese subjects. The extension study will be unblinded so that subjects assigned to the placebo arm (Arm 2) may discontinue treatment with normal saline placebo and have the option of receiving pembrolizumab if there is documented PD by central radiological review.

Details of the analysis will be provided in a separate China-specific sSAP document.

Section 8.2 Responsibility for Analyses/In-House Blinding

For all Chinese subjects, including subjects randomized in the global study and the extension study, subject-level treatment randomization information will be blinded to the statistician(s)/programmer(s) responsible for the China extension study analysis until the extension study database lock is achieved. The extent to which individuals are unblinded to the results will be limited. Blinded and unblinded members will be clearly documented.

Section 8.5.1 Efficacy Analysis Populations

Any subject enrolled in the extension study in China after global enrollment is completed, will be excluded from the ITT population. After enrollment for the global study is completed, the study will continue to randomize subjects in China until the sample size for the Chinese subjects reaches approximately 120 Chinese subjects. Chinese subjects randomized in the extension study will not be included in the above primary efficacy analysis population. The Chinese ITT population 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.

Section 8.9 Sample Size and Power Calculations

After enrollment for the global study is completed, the study will continue to randomize subjects in a 1:1 ratio into the pembrolizumab + chemotherapy arm or saline placebo + chemotherapy arm in China until the sample size for Chinese subjects reaches approximately 120, to evaluate the consistency of efficacy and safety in the Chinese subpopulation compared to the global population. Chinese subjects randomized after completion of enrollment in the global study will not be included in the analysis of the global study.

13.0 SIGNATURES

13.1 Sponsor's Representative

TYPED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	

13.2 Investigator

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

TYPED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	