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TITLE:

A Randomized Open-Label Phase III Trial of Pembrolizumab versus Platinum based Chemotherapy in 1L Subjects with PD-L1 Strong Metastatic Non-Small Cell Lung Cancer

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SUMMARY OF CHANGES

PRIMARY REASON(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
5.2.1.2	Dose Modification (Escalation/Titration/Other)	The guidelines in Table 3 are expanded to cover supportive care, monitoring, and follow-up. Myocarditis is added.	To provide current, comprehensive guidelines for management of immune-related adverse events.
6.1	Pembrolizumab Arm: Treatment and Follow-up Phase	Survival status activities are shown taking place throughout the trial. The frequency of telephone contacts during the Survival Follow-up Phase is changed from every 2 months to approximately every 2 months.	To allow flexibility of survival status activities and ensure that current, complete survival data are available at the time of database locks To allow flexibility of survival status activities
6.2	SOC Arm: Treatment and Follow-up Phase		
6.3	Second Course Treatment and Follow-up Phase		
6.4	Cross Over Phase		

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
6.5	Amendment 08, Pembrolizumab Arm: Treatment and Follow-up Phase	Survival status activities are shown taking place throughout the trial. The frequency of telephone contacts during the Survival Follow-up Phase is changed from every 2 months to approximately every 2 months,	To allow flexibility of survival status activities and ensure that current, complete survival data are available at the time of database locks To allow flexibility of survival status activities
6.6	Amendment 08, SOC Arm: Treatment and Follow-up Phase		
6.7	Amendment 08, Second Course Treatment and Follow-up Phase		
6.8	Amendment 08, Cross Over Phase		
7.1.5.4.2	Survival Follow-up	The frequency of telephone contacts during the Survival Follow-up Phase is changed from every 2 months to approximately every 2 months.	To allow flexibility of survival status activities
7.1.5.7	Survival Status	This section is added to state that the Sponsor may request updated survival data during the course of the trial.	To allow flexibility of survival status activities and ensure that current, complete survival data are available at the time of database locks

ADDITIONAL CHANGE(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
1.0	Trial Summary	Once subjects have achieved the trial objective or the trial has ended, subjects are discontinued from this trial and will be enrolled in an extension trial to continue protocol-defined assessments and treatment.	This trial has been identified to roll over into an extension trial.
2.2	Trial Diagram	The pembrolizumab extension trial after survival follow-up is added. Changes from Amendment 08 are added.	
5.10	Beginning and End of the Trial	Upon trial completion, subjects are discontinued and enrolled in a pembrolizumab extension trial.	
2.1	Trial Design	Serious adverse events (SAEs) and Events of Clinical Interest (ECI) will be collected for up to 90 days following cessation of treatment or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier.	Correction of typographic error
2.1	Trial Design	Reference to the Events of Clinical Interest (ECI) guidance document is removed.	This document has been retired.
4.2.2	Rationale for Dose Selection/Regimen/Modification	The rationale for the pembrolizumab dose of 200 mg every 3 weeks was updated.	Updated clinical and pharmacology data are available.

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
7.1.5.5	Second Course Phase	Subjects randomized to pembrolizumab may be eligible to receive pembrolizumab for 17 cycles in the Second Course Phase of the trial if they experienced progressive disease (PD) during treatment, yet continued to receive pembrolizumab beyond progression and attained subsequent benefit, completing 24 months without further disease progression or intolerability. in the	To allow subjects to enter the Second Course Phase if they experienced PD during treatment but continued receiving pembrolizumab beyond progression and had subsequent benefit, completing 24 months without further progression or intolerability.
2.1	Trial Design	Amendment 06 is changed to Amendment 08.	The previous amendment was Amendment 08.
2.2	Trial Diagram		
6.5	Amendment 08, Pembrolizumab Arm: Treatment and Follow-up Phase		
6.6	Amendment 08, SOC Arm: Treatment and Follow-up Phase		
6.7	Amendment 08, Second Course Treatment and Follow-up Phase		

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
6.8	Amendment 08, Cross Over Phase	Amendment 06 is changed to Amendment 08.	The previous amendment was Amendment 08.
7.1.2.6	Tumor Imaging		
7.1.2.8	Patient Reported Outcomes (PROs)		
7.1.3.2	Pharmacokinetic Evaluations		
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8.1.3	Multiplicity		
8.1.5	ORR, PFS and OS Analyses		
8.2.6	Multiplicity		

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
8.2.7	Sample Size and Power Calculation		
8.2.9	ORR, PFS and OS Analyses		
8.2.9.2	Final OS Analysis	Amendment 06 is changed to Amendment 08.	The previous amendment was Amendment 08.
6.5 6.7 6.8	Amendment 08, Pembrolizumab Arm: Treatment and Follow-up Phase Amendment 08, Second Course Treatment and Follow-up Phase Amendment 08, Cross Over Phase	Footnote 26 corrected to 14, and footnote added. Footnote 16 corrected to 14, and footnote added. Footnote 18 corrected to 16, and footnote added.	Correction.
12.4	List of Abbreviations	The following are added: PD-L1 (Programmed Cell Death Ligand 1) PD-L2 (Programmed Cell Death Ligand 2)	Not previously added

1.0 TRIAL SUMMARY

Abbreviated Title	Pembrolizumab versus SOC in 1L Subjects with PD-L1 Strong Metastatic NSCLC
Trial Phase	Phase III
Clinical Indication	Non-Small Cell Lung Cancer
Trial Type	Interventional
Type of control	Active Control without Placebo
Route of administration	Intravenous
Trial Blinding	Unblinded Open-label
Treatment Groups	Pembrolizumab (MK-3475) 200 mg intravenous (IV) every 3 weeks OR SOC: investigator's choice of one of the following: Gemcitabine 1250 mg/m^2 & Cisplatin 75 mg/m^2 Q3W for 4-6 cycles Gemcitabine 1250 mg/m^2 & Carboplatin AUC 5-6 Q3W for 4-6 cycles Pemetrexed 500 mg/m^2 & Carboplatin AUC 5-6 Q3W for 4-6 cycles followed by optional pemetrexed 500 mg/m^2 Q3W (this arm is permitted for nonsquamous histologies only) Pemetrexed 500 mg/m^2 & Cisplatin 75 mg/m^2 Q3W for 4-6 cycles followed by optional pemetrexed 500 mg/m^2 Q3W (this arm is permitted for nonsquamous histologies only) Paclitaxel 200 mg/m^2 & Carboplatin AUC 5-6 Q3W for 4-6 cycles followed by optional pemetrexed maintenance (pemetrexed maintenance is permitted for nonsquamous histologies only)
Number of trial subjects	Approximately 300 subjects will be enrolled.
Estimated duration of trial	The sponsor estimates that the trial will require approximately 3 years from the time the first subject signs the informed consent until the last subject's last visit.
Duration of Participation	Each subject will participate in the trial for up to 2.5 years from the time the subject signs the Informed Consent Form (ICF) through the final contact. After a screening phase of up to 42 days, eligible subjects can be randomized to either to pembrolizumab or SOC. Subjects will receive assigned treatments during a 3-week (Q3W) dosing cycle (for both the control and pembrolizumab arms). Treatment on study will continue until disease progression, unacceptable adverse event(s), intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw the subject, noncompliance with trial treatment or procedures requirements, the subject receives 35 treatments of study medication (pembrolizumab arm only), or administrative reasons. Subjects on the pembrolizumab arm who attain a complete response may consider stopping trial treatment if they meet criteria for holding therapy. Subjects receiving pembrolizumab who stop drug administration after receiving 35 trial treatments for reasons other than disease progression or intolerability, or subjects who attain a complete response and stop trial treatment may be eligible for retreatment with pembrolizumab upon experiencing disease progression. The decision to retreat will be at the discretion of the investigator only if they meet the criteria for retreatment and the trial is ongoing. Retreatment is limited to 17 cycles. After the end of treatment each subject will be followed for a minimum of 30 days for adverse event (AE) monitoring. Serious adverse events (SAE) and Events of Clinical Interest (ECI) will be collected for up to 90 days following cessation of treatment or 30 days

	following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier. Subjects randomized to the control arm will have the option of receiving treatment with pembrolizumab. Subjects will have post-treatment follow-up for disease status, including initiating a non-study cancer treatment and experiencing disease progression, until death, withdrawing consent, or becoming lost to follow-up. Once subjects have achieved the trial objective or the trial has ended, subjects are discontinued from this trial and will be enrolled in an extension trial to continue protocol-defined assessments and treatment. After marketing approval of pembrolizumab, "clinical trial" will be replaced with "post-marketing clinical trial" and this study will be continued.
Randomization Ratio	1:1

2.0 TRIAL DESIGN

2.1 Trial Design

This is a multicenter, international, randomized, open label, controlled trial of intravenous (IV) pembrolizumab monotherapy versus the choice of multiple standard of care (SOC) platinum based chemotherapies in subjects previously untreated for their Stage 4, Programmed Cell Death Ligand 1 (PD-L1) strong, non-small cell lung cancer (NSCLC). Approximately 300 subjects whose tumors are classified as PD-L1 strong, who lack an epidermal growth factor receptor (EGFR) sensitizing mutation and are anaplastic lymphoma kinase (ALK) translocation negative NSCLC will be enrolled in this trial for examination of the efficacy and safety of pembrolizumab vs SOC chemotherapies. Subjects will be randomized in a 1:1 ratio to receive pembrolizumab or the investigator's choice of one of the platinum doublets listed below:

1) Pemetrexed 500 mg/m^2 every 3 weeks (Q3W) and carboplatin Area Under Curve (AUC) 5-6 day 1 Q3W for 4-6 cycles followed by optional pemetrexed 500 mg/m^2 Q3W (this arm is permitted for nonsquamous histologies only)

2) Pemetrexed 500 mg/m^2 Q3W and cisplatin 75 mg/m^2 day 1 Q3W for 4-6 cycles followed by optional pemetrexed 500 mg/m^2 Q3W (this arm is permitted for nonsquamous histologies only)

3) Gemcitabine 1250 mg/m2 days 1 and 8 and cisplatin 75 mg/m2 day 1 Q3W for 4-6 cycles

4) Gemcitabine 1250 mg/m2 days 1 and 8 and carboplatin AUC 5-6 day 1 Q3W for 4-6 cycles

5) Paclitaxel 200 mg/m^2 Q3W and carboplatin AUC 5-6 day 1 Q 3W for 4-6 cycles followed by optional pemetrexed maintenance (pemetrexed maintenance is permitted for nonsquamous histologies only) (Figure 1)

The specific platinum doublet (including whether pemetrexed maintenance will be offered for those subjects with non-squamous histologies) as well as the dose (for example, AUC 5 OR 6 for carboplatin) to be administered must be identified prior to randomization. Note: while pemetrexed maintenance is optional, it is STRONGLY recommended in subjects with non-squamous histologies and should be administered unless toxicity or decline in performance status precludes its administration, and radiographic imaging does not demonstrate PD after completion of at least 4 cycles of platinum doublet.

Subjects who have received one of the platinum doublets above in the neoadjuvant or adjuvant setting are not permitted to receive the same platinum doublet in this trial if randomized to the control arm, unless a known contraindication prohibits treatment with another platinum doublet. Furthermore, pemetrexed will not be permitted as chemotherapy for subjects with squamous histology. Subjects will be stratified by Eastern Cooperative Oncology Group (ECOG) Performance Scale (0 vs 1), histology (squamous vs non-squamous), and geographic region of the enrolling site (East Asia vs non-East Asia), prior to randomization. The investigator will decide before randomization which chemotherapy regimen a subject would receive in case the subject is assigned to the chemotherapy arm. The subject will then have equal chance to be randomized in the pembrolizumab arm and the chemotherapy arm within the stratification group to which the subject belongs.

Subjects will be evaluated every 9 weeks (63 +/- 7 days) with radiographic imaging to assess response to treatment. All imaging obtained on study will be submitted for a central radiologists' review, which will assess the images using Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 for determination of objective response rate (ORR) and progression-free survival (PFS).

Following amendment 08, imaging will no longer be required as a study procedure and sites will no longer be required to submit imaging for central review.

Subjects should continue with the assigned study treatment until RECIST 1.1-defined progression of disease as assessed by the investigator, unacceptable toxicity, intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw the subject, subject withdraws consent, pregnancy of the subject, noncompliance with trial treatment or procedure requirements, administrative reasons, or the subject has received 35 trial treatments of pembrolizumab. Treatment may continue despite RECIST 1.1 defined progression if the subject is clinically stable and is considered to be deriving clinical benefit by the investigator. Adverse events (AEs) will be monitored throughout the trial and graded in severity according to the guidelines outlined in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

Following amendment 08, subjects assigned to the control arm that meet all crossover criteria outlined in Section 7.1.5.6 will have the opportunity to crossover to pembrolizumab. Section 7.1.5.6 provides crossover criteria and guidance. Treatment is limited to 35 administrations of pembrolizumab during the initial treatment phase; a cross over subject may be treated in a second course phase if they meet criteria outlined in Section 7.1.5.5.

Pembrolizumab treated subjects who attain a confirmed CR may consider stopping trial treatment. These subjects, as well as those subjects assigned to the pembrolizumab arm who stop trial therapy after 35 trial treatments 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 7.1.5.4. Response or progression in the Second Course Phase will not count towards the ORR and PFS of the primary endpoint in this trial.

After the end of treatment, each subject (including subjects randomized to the control arm who opt to receive pembrolizumab) will be followed for a minimum of 30 days for AE monitoring. Serious adverse events (SAEs) and Events of Clinical Interest (ECI) will be collected for up to 90 days following cessation of treatment or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier. Subjects will have post-treatment follow-up for disease status, including initiating a non-study cancer treatment and experiencing disease progression, until death, withdrawing consent, or becoming lost to follow-up. The primary objective of the trial is PFS per RECIST 1.1 by blinded independent central radiologists' review. Secondary objectives include overall survival (OS), ORR per RECIST 1.1 by blinded independent central radiologists' review, and safety as assessed by a variety of parameters of AEs, including ECI with a potential immunologic etiology. . Exploratory analyses include PFS2 (defined as the time from randomization to disease progression on the next line of therapy, or death from any cause, whichever first), ORR per irRC, response duration per RECIST 1.1 by blinded independent central radiologists' review, response duration per irRC, PFS per immune-related response criteria (irRC), and health-related quality-of-life assessments (QoL).

Participation in this trial will be dependent upon supplying tumor tissue from locations that have not been radiated. Formalin-fixed specimens obtained either at the time of or after the subject has been diagnosed with metastatic disease will be required for determination of PD-L1 status. Biopsies obtained PRIOR to receipt of neoadjuvant/adjuvant chemotherapy is NOT permitted. The specimen will be evaluated at a central laboratory facility for expression status of PD-L1 in a prospective manner. Only subjects whose tumors express PD-L1 at a predefined cut point as determined by the central laboratory facility will be eligible for randomization.

Subjects who received neoadjuvant/adjuvant therapy are permitted onto the trial as long as therapy was completed at least 6 months prior to the diagnosis of metastatic disease.

One PFS analysis will be conducted during the course of the trial. The analysis is expected to occur after approximately 175 PFS events per RECIST 1.1 by blinded independent central radiologists' review have occurred in both arms. The purpose of this analysis is to demonstrate superiority of pembrolizumab in PFS and to demonstrate no evidence of a detriment in OS. One hundred and ten OS events are expected to occur at the time of the PFS analysis. OS analyses will also be performed at the final PFS analysis. In addition, the trial may be stopped early at the recommendation of the Data Monitoring Committee (DMC) if

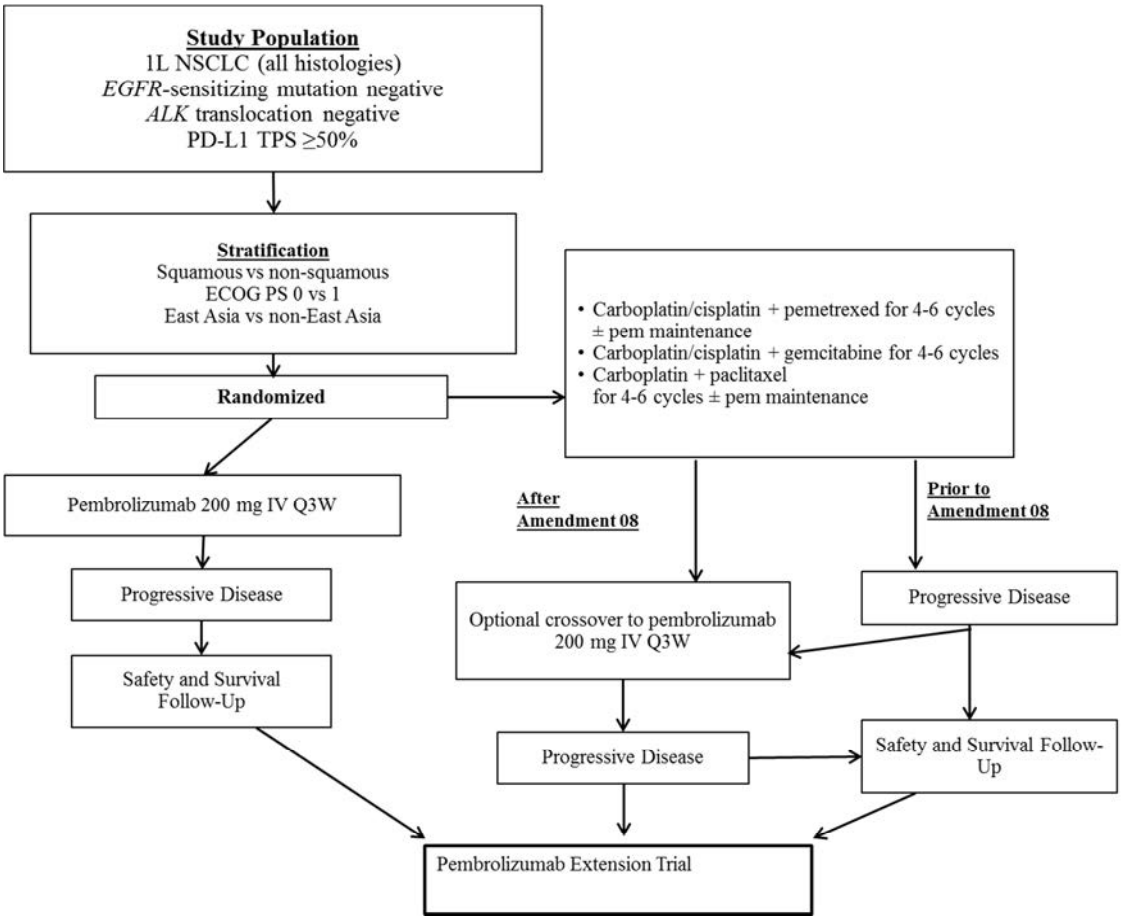
the risk/benefit ratio to the trial population as a whole is unacceptable. Details are described in Section 8.0– Statistical Analysis Plan.

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

After marketing approval of pembrolizumab, "clinical trial" will be replaced with "post-marketing clinical trial" and this study will be continued.

2.2 Trial Diagram

The trial design is depicted in Figure 1 below.



1L= first line; ALK= anaplastic lymphoma kinase; ECOG PS=Eastern Cooperative Oncology Group Performance Status; EGFR=epidermal growth factor receptor; IV=intravenous; NSCLC=non-small cell lung cancer; PD-L1=Programmed Cell Death Ligand 1; pem=pembrolizumab; Q3W=every 3 weeks; TPS=tumor proportion score.

Figure 1 Trial Design

3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

3.1 Primary Objective(s) & Hypothesis(es)

1) **Objective:** To compare the PFS per RECIST 1.1 as assessed by blinded independent central radiologists' review in subjects with PD-L1 strong, 1L metastatic NSCLC treated with pembrolizumab compared to SOC chemotherapies.

   Hypothesis: Pembrolizumab prolongs PFS by RECIST 1.1 (blinded independent central radiologists' review) in subjects with PD-L1 strong NSCLC compared to SOC chemotherapies.

3.2 Secondary Objective(s) & Hypothesis(es)

1) **Objective:** Evaluate the safety and tolerability profile of pembrolizumab in subjects with 1L metastatic PD-L1 strong NSCLC.

2) **Objective**: Evaluate the OS in subjects with 1L metastatic PD-L1 strong NSCLC treated with pembrolizumab compared to SOC chemotherapies.

3) **Objective:** Evaluate the ORR as assessed by RECIST 1.1 by blinded independent central radiology review in subjects with 1L metastatic PD-L1 strong NSCLC treated with pembrolizumab compared to SOC chemotherapies.

   Hypothesis: Pembrolizumab improves the ORR by RECIST 1.1 (blinded independent central radiologists' review) in subjects with PD-L1 strong NSCLC compared to SOC chemotherapies.

3.3 Exploratory Objectives

1) **Objective**: To evaluate PFS per immune-related response criteria (irRC) in subjects with 1L metastatic PD-L1 strong NSCLC treated with pembrolizumab compared to SOC chemotherapies.

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

3) **Objective**: To evaluate ORR per irRC in subjects with 1L metastatic PD-L1 strong NSCLC treated with pembrolizumab compared to SOC chemotherapies.

4) **Objective**: To evaluate response duration per RECIST 1.1 by blinded independent central radiologists' review in subjects with 1L metastatic PD-L1 strong NSCLC treated with pembrolizumab compared to SOC chemotherapies.

5) **Objective**: To evaluate response duration per irRC in subjects with 1L metastatic PD-L1 strong NSCLC treated with pembrolizumab compared to SOC chemotherapies.

6) **Objective**: To evaluate patient-reported treatment effects at pre-specified time points while on treatment and post-discontinuation as measured by changes from baseline in all domains and single items of the QLQ-C30 and LC13, with particular emphasis on QLQ-C30 QoL domain, chest pain (LC13 question 10), cough (LC13 question 1) and dyspnea domain (LC13 questions 3-5) in previously untreated advanced NSCLC subjects receiving either pembrolizumab or comparator.

7) **Objective**: To summarize and compare by treatment arm, the number and proportion of subjects who improved, worsened or remained stable for all domains and single items of the QLQ-C30 and LC13.

8) **Objective**: To describe by treatment arm, the proportion of subjects reporting "no", "some", or "extreme" EQ-5D health state profiles at pre-specified time points.

9) **Objective**: To evaluate within each treatment arm, quality-adjusted survival using the Quality-adjusted Time without Symptoms or Toxicity (Q-TWiST) approach.

10) **Objective**: To evaluate within each treatment arm, the difference in patient reported outcome (PRO) score for progressed subjects compared to subjects with no radiographic evidence of tumor progression.

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

4.0 BACKGROUND & RATIONALE

4.1 Background

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

4.1.1 Pharmaceutical and Therapeutic Background

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

The Programmed Cell Death 1 (PD-1) receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. 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 Programmed Cell Death Ligand 2 [PD-L2]) [40] [41]. The mechanism by which PD-1 down modulates T-cell responses is similar to, but distinct from that of CTLA-4 as both molecules regulate an overlapping set of signaling proteins [42] [34]. PD-1 was shown to be expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B-cells, T regs and Natural Killer cells [43] [44]. The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types, including non-hematopoietic tissues as well as in various tumors [42] [45] [46] [47]. Both ligands are type I transmembrane receptors containing both IgV- and IgC-like domains in the extracellular region and contain short cytoplasmic regions with no known signaling motifs. Binding of either PD-1 ligand to PD-1 inhibits T-cell activation triggered through the T-cell receptor. PD-L1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments. PD-L2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T-cell function in peripheral tissues [45]. Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. High expression of PD-L1 on tumor cells (and to a lesser extent of PD-L2) has been found to correlate with poor prognosis and survival in various cancer types, including RCC [17], pancreatic carcinoma [48], hepatocellular carcinoma [49], and ovarian carcinoma [50]. Furthermore, PD-1 has been suggested to regulate tumor-specific T-cell expansion in subjects with MEL [51].

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 PN 010, the Phase 2/3 trial of pembrolizumab vs docetaxel in previously treated subjects with advanced or metastatic NSCLC.

Anti-mouse PD-1 or anti-mouse PD-L1 antibodies have demonstrated anti-tumor responses as a mono-therapy in models of squamous cell carcinoma, pancreatic carcinoma, MEL and colorectal carcinoma. Blockade of the PD-1 pathway effectively promoted CD8+ T-cell infiltration into the tumor and the presence of IFN-γ, granzyme B and perforin, indicating that the mechanism of action involved local infiltration and activation of effector T-cell function in vivo [48] [52] [53] [54] [55] [56]. In addition, the combination of gemcitabine and anti-PD-L1 mAb demonstrated synergy in the rejection of pancreatic mouse tumors [48]. In-house experiments have confirmed the in vivo efficacy of PD-1 blockade as a mono-therapy as well as in combination with chemotherapy in syngeneic mouse tumor models (see the Investigator Brochure (IB).

Recent clinical data of pembrolizumab suggest high sustained rates of tumor regression in subjects with advanced melanoma. Pembrolizumab was dosed intravenously at a dose of 10 mg per kilogram of body weight every 2 or 3 weeks or 2 mg per kilogram Q3W in subjects with advanced melanoma, including a cohort of subjects who had received prior treatment with the immune checkpoint inhibitor ipilimumab and those who had not. Tumor responses were assessed every 12 weeks. A total of 135 subjects with advanced melanoma were treated. Common AEs attributed to treatment were fatigue, rash, pruritus, and diarrhea; most of the AEs were low grade. The confirmed response rate across all dose cohorts, evaluated by central radiologic review according to the RECIST 1.1, was 38% (95% confidence interval [CI], 25 to 44), with the highest confirmed response rate observed in the cohort that received 10 mg per kilogram every 2 weeks (52%; 95% CI, 38 to 66). The response rate did not differ significantly between subjects who had received prior ipilimumab treatment and those who had not (confirmed response rate, 38% (95% CI, 23 to 55) and 37% (95% CI, 26 to 49), respectively). Responses were durable in the majority of subjects (median follow-up, 11 months among subjects who had a response); 81% of the subjects who had a response (42 of 52) were still receiving treatment at the time of analysis in March 2013. The overall median PFS among the 135 subjects was longer than 7 months. These data indicate that high rates of durable responses are achieved with pembrolizumab in subjects with advanced melanoma irrespective of any prior treatment with an immune checkpoint inhibitor. Furthermore, the toxicity profile was manageable with the majority grade of the toxicities grade 1 or 2. [57]

4.1.2 Ongoing Clinical Trials

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

Protocol 001 (PN001) Part C enrolled 38 subjects with NSCLC (adenocarcinoma, squamous cell carcinoma, and large cell carcinoma) who experienced progression of cancer after initiation of their second line of systemic therapy to receive monotherapy pembrolizumab. By investigator-assessed irRC, the ORR; (confirmed and unconfirmed) was 24%. Similar results were obtained using RECIST 1.1, yielding an ORR (confirmed and unconfirmed) of 21%. Most responses by irRC were observed by the time of first planned assessment at Week 9. The median duration of response by irRC has not been reached with a median duration of follow-up of 62 weeks. The median OS for all 38 subjects treated with pembrolizumab was 51 weeks.

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, the presumptive predictive biomarker of pembrolizumab, using a preliminary immunohistochemistry assay. A modified H-score scoring system of PD-L1 expression was established for NSCLC by

analyzing tumor specimens from resected NSCLC specimens. This scoring system was then applied to the samples from PN001 Part C.

A total of 35 subjects from PN001 had tumor samples evaluable and a clinical response assessed. All but 3 subjects were from Part C; 3 subjects from Part A had NSCLC, submitted tumor tissue, and had a clinical response assessment. Seven of the 35 subjects had a clinical response (20%) by investigator assessed irRC. Six responders (26%) were observed amongst the twenty-three subjects whose tumors expressed PD-L1. Of note, these six responders clustered at the higher end of the modified H-score. Six of nine (67%) subjects whose tumors expressed PD-L1 to an extent above the preliminary cut point had a clinical response. No responses were noted amongst the subjects whose tumors did not express PD-L1.

A training set comprised of approximately 140 tumor samples and their associated clinical outcome data were used to assess an optimal cutpoint for PD-L1 positivity. An optimal PD-L1 cutpoint was identified by receiver operator characteristic curve analyses and by considering clinical implications of false positive and false negative results. Cutpoint was identified based upon a proportions score (PS) method of IHC analysis with the tumors expressing at or greater than the highest cutpoint (PS $\geq$50%) referred to as PD-L1 strong tumors, and tumors expressing $\geq$1% but less than 50% referred to as the PD-L1 weak tumors. Outcomes based in immune related Response Criteria (irRC) were used as the primary outcome for the analysis. Based on the training set, the Positive Predictive Value for subjects in the strong category was 42% while maintaining a negative predictive value of 92% for subjects in the weak or null category. Given the limited activity in PD-L1 weak and negative subjects observed to date, these subjects will be excluded from this trial in 1st line NSCLC subjects.

KEYNOTE 001 Part F enrolled PD-L1 positive, previously untreated subjects with advanced NSCLC (Part F1) or previously treated subjected with advanced NSCLC (Part F2). For the subjects enrolled onto Part F2, the median PFS by investigator assessed irRC was 26.4 weeks in the highest PD-L1 positive cohort (PD-L1 "strong"); the median OS in the same cohort was 13.7 months. Preliminary data from 45 subjects enrolled in KEYNOTE 001, Part F1 (previously untreated, PD-L1 positive NSCLC) indicate an ORR by investigator assessed irRC of 36%. Median OS at 12 months has not been reached with an OS rate at 12 months of 79.7%. Analyses have not been performed to date in the PD-L1 strong cohort enrolled in KEYNOTE 001 Part F1.

4.1.3 Information on Other Trial –Related Therapy

Platinum doublets are the SOC for the treatment of patients with good performance status (ECOG 0 or 1), advanced or metastatic, previously untreated NSCLC patients who lack an EGFR sensitizing (activating) mutation and ALK translocation. These platinum doublets include a platinum compound in combination with gemcitabine, pemetrexed, docetaxel, or bevacizumab. [58] These combinations have demonstrated OS gain, improved quality of life, and control of disease related symptoms compared to single agent regimens, with several combinations demonstrating similar efficacy. As such, the phase 3 trial proposed will offer

multiple platinum combinations as control arm options and will be selected by the investigator prior to randomization.

Approval for gemcitabine in combination with cisplatin was granted based upon data observed in Phase 3 randomized controlled trial of gemcitabine in combination with cisplatin which demonstrated a significant improvement in response rate (30.4% compared with 11.1%, respectively; $p<0.0001$), median time to progressive disease (5.6 months compared with 3.7 months, respectively; $p=0.0013$), and OS (9.1 months compared with 7.6 months, respectively, $p=0.004$), compared to single agent cisplatin. Toxicity was predominantly hematologic (neutropenia and thrombocytopenia), and was more pronounced in the combination arm, with grade 4 neutropenia occurring in 35.3% of subjects compared with 1.2% of subjects on the cisplatin monotherapy arm. [59]

A randomized Phase 3 study of gemcitabine + cisplatin vs gemcitabine + carboplatin (1200 mg/m(2) on Days 1 and 8, followed on Day 1 by cisplatin 80 mg/m(2) or carboplatin AUC=5, each for a maximum of 6 cycles or until disease progression or unacceptable toxicity), in previously untreated Stage 3B and 4 NSCLC subjects demonstrated ORRs, median time to disease progression, response duration and survival of 41/29%, 5.87/4.75 months, 7.48/5.15 months, and 8.75/7.97 months for the gemcitabine/cisplatin and gemcitabine/carboplatin arms, respectively. Toxicity profiles were similar across the two combinations with the only significantly different grade 3/4 toxicities including nausea and vomiting in the gemcitabine + cisplatin combination and thrombocytopenia in the gemcitabine + carboplatin combination [60]. The comparable efficacy and toxicity of these two combinations indicate that either platinum in combination with gemcitabine is acceptable for the treatment of advanced or metastatic, previously untreated NSCLC.

In addition, the Phase 3 trial proposed will offer the choice of pemetrexed in combination with either carboplatin or cisplatin for a maximum of 6 cycles followed by optional pemetrexed maintenance as well as carboplatin in combination with paclitaxel followed by optional pemetrexed maintenance. Pemetrexed will only be permitted in subjects with non-squamous histologies.

The approval of pemetrexed is limited to subjects with NSCLC with non-squamous histology by both the FDA and EMA. The approval was based upon the Phase 3, noninferiority trial in first line, advanced NSCLC subjects that compared the OS of pemetrexed plus cisplatin to gemcitabine plus cisplatin. Overall survival for the cisplatin/pemetrexed was noninferior to the cisplatin/gemcitabine combination with median survivals of 10.3 months in both treatment arms (adjusted hazard ratio [HR] 0.94 [95 percent CI: 0.84, 1.05]). The median PFS was 4.8 and 5.1 months for the pemetrexed + cisplatin and gemcitabine + cisplatin arms, respectively (adjusted HR 1.04 [95 percent CI: 0.94, 1.15]). The overall response rates were 27.1 percent and 24.7 percent for the pemetrexed + cisplatin and gemcitabine + cisplatin arms, respectively. In a pre-specified analysis, OS was statistically superior for the cisplatin/pemetrexed arm in subjects with adenocarcinoma (12.6 vs 10.9 months). In contrast, subjects with squamous cell histology had a significant improvement in OS with the cisplatin/gemcitabine combination (10.8 vs 9.4 months) [61], indicating differential efficacy in histological subtypes of NSCLC.

Further gains in OS have been achieved with the administration of pemetrexed maintenance. A phase 3, double-blind study of maintenance pemetrexed plus best supportive care (BSC) versus placebo plus BSC was conducted in subjects with NSCLC whose disease had not progressed following 4 cycles of cisplatin + pemetrexed induction. Subjects were randomized 2:1 to pemetrexed + BSC or placebo + BSC, which were continued until disease progression or toxicity. The median OS for subjects in the intent-to-treat (ITT) group was 13.4 months for subjects receiving pemetrexed and 10.6 months for those receiving placebo (HR of 0.79 [95 percent CI: 0.65, 0.95, *p*=0.012]). Median OS was 15.5 months versus 10.3 months for subjects with non-squamous NSCLC receiving pemetrexed or placebo, respectively (HR of 0.70 [95 percent CI: 0.56, 0.88]). The median OS in subjects with squamous cell NSCLC receiving pemetrexed was 9.9 months versus 10.8 months for those receiving placebo (HR of 1.07 [95 percent CI: 0.77,1.50])[62]. These findings have established pemetrexed maintenance following completion of 4 cycles of a platinum doublet induction as a safe and efficacious regimen in patients with advanced or metastatic non-squamous NSCLC.

While the reciprocal use of carboplatin and cisplatin was demonstrated by Sandler and colleagues when combined with gemcitabine [59], 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 percent CI: 0.99 t, 1.15, *p*=0.100). In addition, the random-effects survival model gave an estimated value of the HR of mortality equal to 1.08 (95 percent CI: 1.00, 1.16, *p*=0.063). Toxicity data indicated that carboplatin based doublets caused more thrombocytopenia, while cisplatin-based chemotherapy caused more nausea, vomiting and renal toxicity. The incidence of neurotoxicity was not different in the two treatments groups. These data indicate that while a trend for improved efficacy is observed with cisplatin based chemotherapies, the results are not statistically significant and are associated with an increased incidence of SAEs. [63] These data support the interchangeable use of carboplatin or cisplatin in combination with SOC antineoplastic agents and should be offered as options for the treatment of advanced or metastatic NSCLC patients that have not previously received systemic cytotoxic therapies for their metastatic disease.

The platinum containing regimen of carboplatin in combination with paclitaxel will also be included as a control chemotherapy option. Multiple Phase 3 studies have demonstrated similar efficacy for carboplatin plus paclitaxel compared to other platinum doublets, including ECOG 1594 [64]. This is especially significant given that treatment options are limited for squamous histologies. As such, KEYNOTE 024, as planned, will additionally allow paclitaxel 200 mg/m2 in combination with carboplatin AUC 5 or 6, both IV, dosed every three weeks for a maximum of 6 cycles as a control, chemotherapy option, followed by pemetrexed maintenance if the investigator chooses, in subjects with non-squamous histologies.

Bevacizumab containing regimens will not be included among the SOC treatment options in the Phase 3 trial proposed for multiple reasons, including a significant adverse toxicity profile as well as multiple exclusion criteria limiting the number of subjects eligible for treatment.

AVAiL, a pivotal Phase 3, demonstrated improved PFS of both a low and high dose of bevacizumab in combination with gemcitabine and cisplatin. Overall survival was not statistically significant. E4599, a pivotal Phase 3, demonstrated improved OS of bevacizumab in combination with carboplatin and paclitaxel. In both studies, subjects with squamous cell histology were excluded from the trial. Furthermore, the incidence of serious AEs was higher in the bevacizumab combinations and included pulmonary hemorrhage, sometimes fatal, as well as other clinically significant manifestations of bleeding. To our knowledge, no randomized controlled trials have been conducted which compare the combinations of carboplatin, paclitaxel, and bevacizumab followed by bevacizumab maintenance to cisplatin and pemetrexed followed by pemetrexed maintenance. Although OS gains may be similar between the two regimens, the risk-benefit profile favors the platinum in combination with pemetrexed followed by pemetrexed maintenance as a treatment option for non-squamous, NSCLC subjects.

The above data support multiple platinum containing chemotherapy comparators as control options and include paclitaxel, gemcitabine, and pemetrexed containing platinum regimens. These control options all have proven clinical benefit in a population with significant unmet need. The further allowance of either cisplatin or carboplatin in combination with pemetrexed and gemcitabine will allow the investigator to choose an appropriate regimen based upon the subject's underlying histology and co-morbidities prior to randomization.

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

Lung cancer had the highest incidence of malignancies globally in 2008 with more than 1.6 million cases. Mortality from lung cancer in 2008 was similar with over 1.4 million deaths from lung cancer globally [65]. NSCLC accounts for approximately 85% of all lung cancer cases.

Progress has been made in the clinical management of early stage NSCLC by establishing comprehensive, multi-modality treatment regimens; however, the prognosis for advanced disease has not improved substantially. With an overall 5-year survival rate of 9% to 13%, the treatment of NSCLC remains a highly unmet medical need. Cytotoxic chemotherapy as single agents or in combination have served as the mainstay of treatment for decades with platinum containing doublets and maintenance strategies conferring the greatest advances in OS gains.

Platinum-based combination chemotherapy prolongs survival, improves quality-of-life, and controls disease related symptoms. Platinum chemotherapy, thus, is the backbone treatment for initial (first line) treatment of patients not candidates for treatment with tyrosine kinase

inhibitors (TKIs) and who have an ECOG PS of 0 or 1. Single agent cytotoxic agents such as gemcitabine or docetaxel are considered SOC for patients with an ECOG PS of 2. Approved therapies for previously untreated, advanced/metastatic NSCLC patients who lack an EGFR sensitizing mutation and are ALK translocation negative include paclitaxel, gemcitabine, docetaxel, pemetrexed and bevacizumab, all in combination with platinum based chemotherapy. While ECOG 1594 demonstrated that the four platinum-doublets tested (cisplatin combined with either paclitaxel, gemcitabine, or docetaxel, and carboplatin and paclitaxel) have equivalent activity in the first-line setting [64], neither pemetrexed nor bevacizumab is appropriate for patients with squamous histology [61] [66] [67]

Recently, targeted therapies for specific tumor genetic alterations have resulted in higher response rates in specific subpopulations of NSCLC patients. Examples include inhibitors against the EGFR family and the ALK. Because of the highly significant demonstration of clinical benefit in these molecularly defined sub-populations, ESMO and NCCN guidelines indicate that first-line treatment with an approved TKI, should be prescribed to patients with tumors bearing an activating (sensitizing) EGFR mutation because of significantly higher response rate (RR), longer PFS, and better quality of life (QoL) (ESMO) when compared with first-line chemotherapy. [58] Recently, a third EGFR inhibitor, afatinib, was approved for the treatment of EGFR inhibitor (TKI) naïve patients with advanced or metastatic NSCLC who bear EGFR activating mutations on the basis of a significantly improved PFS and acceptable safety, as compared to a SOC platinum doublet of cisplatin + pemetrexed. The composite of data demonstrated a favorable benefit-risk ratio and thus contributes to the arsenal of options for NSCLC patients who harbor EGFR activating mutations.

Furthermore, recent retrospective analyses indicate that continuation of TKI treatment beyond RECIST defined progression is associated with a significantly improved OS as compared to subjects who were switched to cytotoxic chemotherapies at the time of RECIST defined PD [68]. The ongoing single arm, Phase 2 ASPIRATION trial (NCT01310036) aims to prospectively determine if continuation of erlotinib beyond RECIST defined progression in Asian subjects with EGFR mutations confers clinical benefit. To our knowledge, no randomized studies comparing treatment beyond progression to the traditional paradigm in which cytotoxic chemotherapy is initiated at the time of progression have been performed. Despite these definitive data, the NCCN guidelines recommend that EGFR inhibitors be continued despite PD in asymptomatic patients who harbor EGFR sensitizing mutations, further underscoring the potential to slow the rate progression and ultimately provide clinical benefit in a patient population with limited therapeutic options in the 2L and beyond.

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

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

Patients who harbor EGFR sensitizing mutations and/or ALK translocations will be excluded from this study. Significant preclinical and clinical data indicate that activation of these respective pathways fundamentally alter the natural history of tumors that bear these

mutations as compared to tumors that do not, which ultimately affect sensitivity to SOC chemotherapies including pemetrexed in the case of ALK translocations [69]. In addition, EGFR sensitizing mutations confer significant prognostic implications as illustrated by the improved PFS to the SOC platinum doublet, carboplatin and paclitaxel, and OS in the EGFR sensitizing mutation population [70]. These mutations also potentially alter PD-L1 expression, likely due to yet undefined interactions between the PD-1/PD-L1/2, EGFR, and EML4/ALK pathways [71]. These observations indicate that tumors that bear EGFR sensitizing mutations or ALK translocations may be fundamentally different from tumors that do not bear these mutations and may have a different safety and efficacy profile with pembrolizumab as compared to tumors that do not bear these mutations. Given that little data exist regarding the safety and/or efficacy implications of pembrolizumab on these tumors, tumors that bear these mutations will be excluded from this study.

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

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.

4.2.1.1 Benefit Risk

The clinical outlook of patients with metastatic, previously untreated NSCLC is bleak with median OSs of approximately 1 year. Survival estimates are especially bleak for patients who do not harbor EGFR sensitizing mutations and ALK translocations, for whom targeted therapies do not exist. Patients that do not have an EGFR sensitizing mutation and/or do not harbor an ALK translocation are treated with SOC platinum doublets. The majority of patients treated with SOC platinum doublets experience early disease progression, significant grade 3 or 4 toxicity, and succumbs to their disease because of the lack of curative therapies in this setting. Thus, there is an urgency to develop new agents for this patient population.

Results from KEYNOTE -001, a large Phase 1 study with multiple Phase 1B like NSCLC cohorts indicate that sustained responses are achieved in patients with metastatic or recurrent NSCLC who express PD-L1 by immunohistochemistry. Preliminary data in 159 pretreated, advanced/metastatic NSCLC patients indicate that pembrolizumab is associated with a 23% ORR by centrally assessed RECIST in PD-L1 positive patients as compared to only a 9% ORR by centrally assessed RECIST in PD-L1 negative patients. Furthermore, the DCR (disease control rate) was 42% in the PD-L1 positive cohort with a median response duration of 7.4 months.

Preliminary safety data indicate that pembrolizumab has an acceptable AE profile. The most common drug related AEs observed in the previously treated cohort described above included fatigue, arthralgia, decreased appetite, pruritus, diarrhea, nausea, pyrexia, rash and hypothyroidism, with the majority being grade 1-2 in severity. Rates of any grade 3-5 drug related AEs were ~ 10%. Immune related AE, including serious AEs, can occur. Based on these preliminary data, the on-going studies (KEYNOTE-001, KEYNOTE-010 and

KEYNOTE-024) and planned study (KEYNOTE-042) are expected to provide confirmatory data demonstrating clinical benefits with pembrolizumab.

In conclusion, pembrolizumab demonstrates a very promising anti-cancer activity in NSCLC patients with an acceptable safety profile compared to those of existing therapeutic options. On-going and planned studies will allow for a more comprehensive analysis of benefit/risk balance of pembrolizumab.

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 pembrolizumab development program, 200 mg Q3W is the appropriate pembrolizumab dose across all indications, and regardless of tumor type. As outlined below, this dose is justified by:

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

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

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

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

4.2.3 Rationale for Endpoints

4.2.3.1 Efficacy Endpoints

Primary: Progression free survival is an acceptable measure of clinical benefit for a randomized Phase 3 trial that demonstrates superiority of a new antineoplastic therapy, especially if the magnitude of effect is large and the therapy has an acceptable risk-benefit profile. Furthermore, it is an endorsed regulatory endpoint for 1L NSCLC trials with recent FDA and EMA approvals including the EGFR inhibitors afatinib and erlotinib. PFS will be assessed by RECIST 1.1 by an independent central radiologists' review which will be blinded to treatment assignment so as to minimize any bias in the response assessments.

Secondary: Overall survival will be included as it is a standard assessment of clinical benefit in subjects with advanced or metastatic NSCLC. Achieving superiority in OS, however, is likely to be limited by dilution of benefit with multiple post-progression therapies as well as optional, planned crossover to pembrolizumab available to subjects randomized to the SOC arm. ORR by RECIST 1.1 criteria as assessed by blinded independent central radiology review and the duration of response by RECIST 1.1 as assessed by blinded independent central radiologists' review will serve as additional measures of efficacy.

Patient Reported Outcomes: EORTC QLQ-C30 version 3.0 and EORTC QLQ-LC13 will be used to investigate (i) quality of life and (ii) disease related symptoms. They are not pure efficacy or safety endpoints because they are affected by both disease progression and treatment tolerability. EQ-5D-3L will be used to calculate health utilities for incorporation into QTWiST and health economic models.

4.2.3.2 Patient Reported Outcomes Instruments

EORTC QLQ-C30 was developed to assess the quality of life of cancer subjects. It has been translated and validated into 81 languages and used in more than 3,000 studies worldwide. It contains 5 functioning scales (physical, role, cognitive, emotional, and social), 3 symptom scales (fatigue, nausea, pain) and additional single symptom items. It is scored on a 4 point scale (1=not at all, 2=a little, 3= quite a bit, 4=very much). The EORTC QLQ-C30 instrument also contains 2 global scales that use 7 point scale scoring with anchors (1=very poor and 7=excellent).

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

The eEuroQol-5D (eEQ-5D) is a standardized instrument for use as a measure of health outcome. The eEQ-5D-3L will provide data for use in economic models and analyses including developing health utilities or QALYs. The five health state dimensions in this instrument include the following: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression (5). Each dimension is rated on a three point scale from 1 (extreme problem) to 3 (no problem). The eEQ-5D will always be completed by subjects first before completing the eEORTC QLQC30 and eEORTC QLQ-LC13.

4.2.3.3 Planned Exploratory Biomarker Research

Additional biomarker research to identify factors important for pembrolizumab therapy will be pursued. Tumor and blood samples may undergo additional proteomic, genomic and transcriptional analyses (both DNA and RNA analyses). This additional biomarker or genomic research may be conducted to identify factors important for pembrolizumab therapy and subject response to therapy (for example, to identify risk factors for AEs or who might best respond to treatment).

4.2.3.4 Future Biomedical Research

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

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

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

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

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

5.1.2 Subject Inclusion Criteria

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

1. Have a histologically or cytologically confirmed diagnosis of NSCLC, is stage IV, does not have an EGFR sensitizing (activating) mutation or ALK translocation, and has not received prior systemic chemotherapy treatment for their metastatic NSCLC.

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

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

4. Have a life expectancy of at least 3 months

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

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

Table 1 Adequate Organ Function Lab Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1,500 /mcL
Platelets	≥100,000 / mcL
Hemoglobin	≥9 g/dL or ≥5.6 mmol/L– without transfusions within 2 weeks of first dose
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	
Total bilirubin	≤ ULN
AST (SGOT) and ALT (SGPT)	≤ 1.5 X ULN
Alkaline Phosphatase	≤ 2.5 X ULN
Endocrine	
Thyroid stimulating hormone (TSH)	Within normal limits. Please note: If TSH is not within normal limits at baseline, the subject may still be eligible if T3 and free T4 are within the normal limits.
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT)	≤1.5 X ULN unless the subject is receiving anticoagulant therapy
Activated Partial Thromboplastin Time (aPTT)	≤1.5 X ULN unless the subject is receiving anticoagulant therapy
[a] Creatinine clearance should be calculated per institutional standard. If no local guideline is available, Creatinine Clearance should be calculated using the Cockcroft-Gault Method: CrCl = ((140-age) * weight (kg) * (0.85 for females only)) / (72 * creatinine)	

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

8. Have provided a formalin fixed tumor tissue sample from a biopsy of a tumor lesion either at the time of or after the diagnosis of metastatic disease has been made AND from a site not previously irradiated to assess for PD-L1 status. Biopsies obtained PRIOR to the administration of any systemic therapy administered for the treatment of a subject's tumor (such as neoadjuvant/adjuvant therapy) will not be permitted for analysis. The tissue sample must be received by the central vendor prior to randomization. Fine needle aspirates, Endobronchial Ultrasound (EBUS) or cell blocks are not acceptable. Needle or excisional biopsies, or resected tissue is required.

9. The subject's tumor does not harbor an EGFR sensitizing (activating) mutation or ALK translocation. EGFR sensitizing mutations are those mutations that are amenable to treatment with tyrosine kinase inhibitors including erlotinib, gefitinib, or afatanib. Investigators must be able to produce the source documentation of the EGFR mutation and ALK translocation status in all subjects with non-squamous histologies AND for subjects in whom testing is clinically recommended. If either an EGFR sensitizing mutation or ALK translocation is detected, additional information regarding the mutation status of the other molecule is not required. If unable to test for these molecular changes, formalin fixed paraffin embedded tumor tissue of any age should be submitted to a central laboratory designated by the Sponsor for such testing. Subjects with non-squamous histologies will not be randomized until the EGFR mutation status and/or ALK translocation status is available in source documentation at the site. For patients enrolled who are known to have a tumor of predominantly squamous histology, molecular testing for EGFR and ALK translocation will not be required as this is not SOC and is not part of current diagnostic guidelines.

10. Have a PD-L1 strong tumor as determined by IHC at a central laboratory.

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

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

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

    c. Whose status is post hysterectomy, oophorectomy or tubal ligation. Documented hysterectomy or oophorectomy must be confirmed with medical records of the actual procedure or confirmed by an ultrasound. Tubal ligation must be confirmed with medical records of the actual procedure otherwise the subject must be willing to use two adequate barrier methods throughout the study, starting with the screening visit through 120 days after the last dose of study therapy and up to 180 days after last dose of chemotherapeutic agents as specified in the protocol. Please see Section 5.7.2 for a list of acceptable birth control methods. Information must be captured appropriately within the site's source documents.

12. If of childbearing potential, female subjects must be willing to use two adequate barrier methods throughout the study, starting with the screening visit through 120 days after the last dose of study therapy and up to 180 days after last dose of chemotherapeutic agents as specified in the protocol. Please see Section 5.7.2 for a list of acceptable birth control methods.

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

13. Male subjects with a female partner(s) of child-bearing potential must agree to use two adequate barrier methods throughout the trial starting with the screening visit through 120 days after the last dose of pembrolizumab is received. Such methods of contraception, or abstinence from heterosexual activity, are required from the screening visit (Visit 1) through 180 days after the last dose of chemotherapy. Males with pregnant partners must agree to use a condom; no additional method of contraception is required for the pregnant partner.

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

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

5.1.3 Subject Exclusion Criteria

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

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

2. Has received systemic therapy for the treatment of their stage IV NSCLC. Completion of treatment with chemotherapy and/or radiation as part of neoadjuvant/adjuvant therapy is allowed as long as therapy was completed at least 6 months prior to the diagnosis of metastatic disease.

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

4. Tumor specimen is not evaluable for PD-L1 expression by the central laboratory. If an additional tumor specimen is submitted AND evaluable for PD-L1 expression, the subject will be eligible to participate if PD-L1 expression is assessed as “strong” by the central laboratory.

5. Is receiving systemic steroid therapy < 3 days prior to the first dose of trial treatment or receiving any other form of immunosuppressive medication (corticosteroid use on study for management of ECIs, as pre-medication for the control chemotherapies, and/or a pre-medication for IV contrast allergies/reactions is allowed). Subjects who are receiving daily steroid replacement therapy serve as an exception to this rule. Daily prednisone at doses of 5-7.5 mg is an example of replacement therapy. Equivalent hydrocortisone doses are also permitted if administered as a replacement therapy.

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

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

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

9. Has untreated central nervous system (CNS) metastases and/or carcinomatous meningitis identified either on the baseline brain imaging (please see Brain Imaging in Section 7 and Site Imaging Manual for additional details on the imaging modality) obtained during the screening period OR identified prior to signing the ICF. Subjects whose brain metastases have been treated may participate provided they show radiographic stability (defined as 2 brain images, both of which are obtained after treatment to the brain metastases. These imaging scans should both be obtained at least four weeks apart and show no evidence of intracranial progression). In addition, any neurologic symptoms that developed either as a result of the brain metastases or their treatment must have returned to baseline or resolved. Any steroids administered as part of this therapy must be completed at least three days prior to study medication.

10. Active autoimmune disease that has required systemic treatment in past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (i.e., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.

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

12. Has interstitial lung disease (ILD) OR has had a history of pneumonitis that has required oral or IV steroids.

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

14. Has an active infection requiring IV systemic therapy.

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

16. Has known active Hepatitis B, Hepatitis C or tuberculosis. 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.

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

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

19. Is, at the time of signing informed consent, a regular user (including "recreational use") of any illicit drugs or had a recent history (within the last year) of substance abuse (including alcohol).

20. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the screening visit (Visit 1) through 120 days after the last dose of pembrolizumab or 180 days after the last dose of SOC chemotherapy.

21. Is or has an immediate family member (spouse or children) who is investigational site or sponsor staff directly involved with this trial, unless prospective IRB approval (by chair or designee) is given allowing exception to this criterion for a specific subject.

5.2 Trial Treatment(s)

The treatments to be used in this trial are outlined below in Table 2. For the control chemotherapy options, the choice of platinum doublet and the respective dose of each chemotherapeutic agent must be made and recorded prior to randomization. If a subject received a platinum doublet as part of neoadjuvant/adjuvant therapy that doublet may not be chosen as a SOC chemotherapy control option for this trial unless a contraindication precludes treatment with an alternate regimen. Pemetrexed is not permitted as a treatment for subjects with squamous histologies.

Table 2 Trial Treatment

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/ Treatment Regimen
Pembrolizumab	200 mg IV	Q3W	IV	Day 1 of each 21 day cycle
Paclitaxel	200 mg/m^2	Q3W	IV	Day 1 of each 21 day cycle
Carboplatin	AUC 5 or 6	Q3W	IV	Day 1 of each 21 day cycle
Pemetrexed	500 mg/m^2	Q3W	IV	Day 1 of each 21 day cycle
Cisplatin	75 mg/m^2	Q3W	IV	Day 1 of each 21 day cycle
Gemcitabine	1250 mg/m^2	Q3W	IV	Day 1 and 8 of each 21 day cycle

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

All supplies indicated in Table 2 above will be provided centrally by the Sponsor or locally by the trial site, subsidiary or designee, depending on local country operational or regulatory requirements.

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

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

5.2.1 Dose Selection/Modification

5.2.1.1 Dose Selection (Preparation)

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

This study will use a fixed dose of 200 mg of pembrolizumab. Details on the dose calculation, preparation and administration are provided in the Pharmacy Manual.

Gemcitabine, carboplatin, cisplatin, paclitaxel and pemetrexed will be prepared and administered as per the approved product label.

5.2.1.2 Dose Modification (Escalation/Titration/Other)

Gemcitabine/Carboplatin or Cisplatin Chemotherapy Regimen

Refer to approved product labels for subjects receiving this regimen

Subjects have the option, in the event of toxicity, to change the choice of platinum (carboplatin and cisplatin) administered. Changes may not occur with the other chemotherapeutic agents provided in this trial.

Pemetrexed/Carboplatin or Cisplatin Chemotherapy Regimen

Refer to approved product labels for subjects receiving this regimen.

Subjects have the option, in the event of toxicity, to change the choice of platinum (carboplatin and cisplatin) administered. Changes may not occur with the other chemotherapeutic agents provided in this trial.

Paclitaxel/Carboplatin and Optional Pemetrexed Chemotherapy Regimen

Refer to approved product labels for subjects receiving this regimen.

Pembrolizumab

If a dose of pembrolizumab is withheld for toxicity, then subjects may resume dosing with pembrolizumab if that is appropriate at their next scheduled appointment or when toxicity has improved as described below.

Pembrolizumab will be withheld for ≥ Grade 3 drug-related toxicity including laboratory abnormalities, and severe or life-threatening AEs as per Table 3 below.

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

General instructions:

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

Immune-related AEs	**Toxicity grade or conditions (CTCAEv4.0)**	**Action taken to pembrolizumab**	**irAE management with corticosteroid and/or other therapies**	**Monitor and follow-up**
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor subjects for signs and symptoms of pneumonitis • Evaluate subjects with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment • Add prophylactic antibiotics for opportunistic infections
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor subjects for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus). • Subjects with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. • Subjects with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
	Grade 4	Permanently discontinue		

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

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

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

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

In case toxicity does not resolve to Grade 0-1 within 12 weeks after last infusion, trial treatment should be discontinued after consultation with the Sponsor. Subjects who require corticosteroids to manage drug-related AEs must be at an equivalent dose of ≤10mg per day of prednisone to resume dosing with pembrolizumab. Furthermore, an inability to reduce the corticosteroid dose for managing a drug-related AE to the equivalent of ≤10 mg prednisone per day within 12 weeks of last pembrolizumab dose should prompt discussion between the investigator and Sponsor regarding the subject's ability to continue on treatment in the trial. With investigator and Sponsor agreement, subjects with a laboratory AE still at Grade 2 after 12 weeks may continue treatment in the trial only if asymptomatic and controlled. This includes subjects who experience drug induced hypothyroidism requiring replacement therapy. Resumption of pembrolizumab may occur once the subject is stable on adequate doses of replacement therapy and is clinically asymptomatic.

For information on the management of AEs, see Section 5.6.1.

Subjects who experience Grade 3 or 4 pneumonitis, or recurrent persistent (>4 weeks) Grade 2 drug-related pneumonitis after rechallenge from a prior episode of persistent (>4 weeks) Grade 2 drug-related pneumonitis, pembrolizumab MUST be permanently discontinued.

For subjects who experience a recurrence of the same AE(s) at the same grade or greater with rechallenge of pembrolizumab, a consultation between the Sponsor and investigator should occur to determine whether the subject should continue in the trial. However, for a subject who experiences a recurrence of the same SAE at the same grade or greater with rechallenge of pembrolizumab, the subject MUST discontinue study medication.

Dose increase or decrease of pembrolizumab will not be permitted in individual subjects.

5.2.2 Timing of Dose Administration

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

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

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

Pembrolizumab: pembrolizumab 200 mg will be administered as a 30 minute IV infusion Q3W. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min).

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

Carboplatin: Carboplatin AUC 5 or 6 will be administered as an IV infusion over 30-60 minutes day 1 of every three week cycle following paclitaxel or pemetrexed infusions.

Cisplatin: Cisplatin 75 mg/m2 will be administered as an IV infusion over 6-8 hours OR as outlined in local standard practices on day 1 of every 3 week cycle following pemetrexed.

Pemetrexed: Pemetrexed 500 mg/m2 will be administered as an IV infusion over 10 minutes every three weeks. All subjects should be pre-medicated with steroids as per approved label and local standard practices. In addition, all subjects assigned to pemetrexed must take a folic acid preparation or multivitamin with folic acid containing between 350 to 1000 mcg daily. At least 5 daily doses of folic acid must be taken during the 7-day period preceding the first dose of pemetrexed and dosing should continue during the full course of therapy and for 21 days after the last dose of pemetrexed.

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

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

Gemcitabine: Gemcitabine 1250 mg/m2 will be administered as an IV infusion over 30 minutes on days 1 and 8 of every 3 week cycle.

Paclitaxel: Paclitaxel 200 mg/m2 will be administered as an IV infusion over 3 hrs. (or per local standard practice) on day 1 of every 3 week cycle and should precede infusion with carboplatin.

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

5.2.3 Trial Blinding/Masking

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

5.3 Randomization or Treatment Allocation

Randomization will occur centrally using an interactive voice response system / integrated web response system (IVRS/IWRS). There are 2 treatment arms. Subjects will be assigned randomly in a 1:1 ratio to pembrolizumab and SOC, respectively. The specific SOC platinum doublet as well as the dose to be administered must be identified prior to randomization.

5.4 Stratification

Randomization will be stratified according to the following factors:

1. Geography: East Asia vs non-East Asia
2. ECOG PS: 0 vs 1.
3. Histology: squamous vs non-squamous

5.5 Concomitant Medications/Vaccinations (Allowed & Prohibited)

5.5.1 Acceptable Concomitant Medications

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

Palliative and supportive care is permitted during the course of the trial for underlying medical conditions and management of symptoms. Surgery for tumor control or symptom management is not permitted during the study. Palliative radiotherapy is permitted to a single lesion if considered medically necessary by the treating physician. Trial therapy should be held during the course of palliative radiotherapy and should be resumed no earlier than the next scheduled administration of trial therapy. The specifics of the radiation treatment, including the location, will be recorded.

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

5.5.2 Prohibited Concomitant Medications and/or Treatments

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

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

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

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

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

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

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

5.6 Rescue Medications & Supportive Care

5.6.1 Supportive Care Guidelines

Pembrolizumab

Pembrolizumab subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator including but not limited to the items outlined below. For additional guidance and/or treatment recommendation please refer to the separate Events of Clinical Interest Guidance Document. For guidelines for continuing treatment with pembrolizumab, see Section 5.2.

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

- Nausea/vomiting: Administration of prophylaxis for nausea and vomiting should be administered per institutional guidelines and local standard practices for the standard of care chemotherapies offered for the control arm. For pembrolizumab, the therapy is considered to be of low to moderate emetogenic potential. Consideration for chemo induced nausea and vomiting prophylaxis should be given in subsequent cycles of the administration according to standard institutional practice and should not be routinely administered prior to the initial trial treatment of pembrolizumab. Subjects should be strongly encouraged to maintain liberal oral fluid intake.

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

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

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

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

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

5.6.1.1 Supportive Care Guidelines for Events of Clinical Interest and Immune-related Adverse Events

Immune-related Adverse Events

Adverse events (both non-serious and serious) associated with drug exposure and consistent with an immune phenomenon may represent an immunologic etiology. These immune related adverse events (irAEs) may be predicted based on the nature of the pembrolizumab compound, its mechanism of action, and reported experience with immunotherapies that have a similar mechanism of action. An irAE can occur shortly after the first dose or several months after the last dose of treatment. Particular attention should be paid to AEs that may be suggestive of potential irAEs as outlined in 7.2.3.2. Information on how to identify and evaluate irAEs has been developed and is included in the Event of Clinical Interest Guidance Document located in the Administrative Binder.

Events of Clinical Interest (ECI)

Events of clinical interest are non-serious and SAEs that may or may not be irAEs. ECIs must be reported to Merck within 24 hours regardless of attribution to study treatment. Of note, the requirement for reporting of ECIs applies to all arms, including comparators, of pembrolizumab clinical trials. Information on how to identify and report ECIs can be referenced in both Section 7.2.3.2 and the Event of Clinical Interest Guidance Document.

5.6.2 Overview of Guidelines for Managing Suspected Pneumonitis from Pembrolizumab

Please consult the Event of Clinical Interest Guidance document in the Administrative Binder for this study for a more in depth discussion of pneumonitis.

5.6.3 Guidelines for Infusion Reactions

Pembrolizumab

Acute infusion reactions (which can include cytokine release syndrome, angioedema, or anaphylaxis) are different from allergic/hypersensitive reactions, although some of the manifestations are common to both AEs. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Signs/symptoms may include: Allergic reaction/hypersensitivity (including drug fever); Arthralgia (joint pain); Bronchospasm; Cough; Dizziness; Dyspnea (shortness of breath); Fatigue (asthenia, lethargy, malaise); Headache; Hypertension; Hypotension; Myalgia (muscle pain); Nausea; Pruritus/itching; Rash/desquamation; Rigors/chills; Sweating (diaphoresis); Tachycardia; Tumor pain (onset or exacerbation of tumor pain due to treatment); Urticaria (hives, welts, wheals); Vomiting.

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

Table 4 Pembrolizumab Infusion Reaction Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 hrs	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g. from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.	Subject may be premedicated 1.5h (± 30-minutes) prior to infusion of pembrolizumab with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of analgesic).
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. Subject is permanently discontinued from further trial treatment administration.	No subsequent dosing
Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For Further information, please refer to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE) at http://ctep.cancer.gov		

5.7 Diet/Activity/Other Considerations

5.7.1 Diet

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

5.7.2 Contraception

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

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

5.7.3 Use in Pregnancy

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

outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor. If a male subject impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to the Sponsor and followed as described above and in Section 7.2.2.

5.7.4 Use in Nursing Women

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

5.8 Subject Withdrawal/Discontinuation Criteria

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

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

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

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

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

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

- Disease progression unless the subject is considered to be deriving clinical benefit by the investigator and is clinically stable.

  Clinical Stability is defined as:

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

  2) No decline in ECOG performance status.

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

- Note: Tumor assessments should continue every 9 weeks (+/- 7 days) until RECIST 1.1-defined disease progression has been established by investigator assessment.
- Unacceptable adverse experiences as described in Section 5.2.1.2.
- Two years of uninterrupted delivery of pembrolizumab Q3W and no documented progression of disease, or 35 administrations of study medication, whichever is later
- Inter-current illness that prevents further administration of treatment
- Investigator's decision to withdraw the subject
- The subject has a confirmed strong serum pregnancy test
- Noncompliance with trial treatment or procedure requirements
- The subject is lost to follow-up
- Administrative reasons

If a pembrolizumab treated subject attains a CR, has been treated for at least six months with pembrolizumab, and has at least two treatments with pembrolizumab beyond the date when the initial CR was declared OR the subject has received the maximum administrations of pembrolizumab as outlined above, the subject and Investigator may consider stopping therapy with pembrolizumab. Subjects who discontinue pembrolizumab and then experience radiographic disease progression according to RECIST 1.1 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. Subjects will resume therapy at the dose and schedule they previously received prior to stopping trial treatment.

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

- The End of Treatment and Follow-up visit procedures are listed in Section 6 – Trial Flow Chart and Section 7.1.5 - Visit Requirements. After the end of treatment, each subject will be followed for a minimum of 30 days for AE monitoring (SAEs/ECIs will be collected for up to 90 days following cessation of treatment or 30 days following cessation of treatment if the subject initiates new anticancer therapy, as described in Section 7.2.3.1). Subjects will have post-treatment follow-up for disease status until disease progression, initiating a non-study cancer treatment, withdrawing consent, becoming lost to follow-up or entering the Second Course Phase. After documented disease progression and/or cessation of treatment with pembrolizumab, each subject will be followed for OS until death or withdrawal of consent.

5.9 Subject Replacement Strategy

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

5.10 Beginning and End of the Trial

The overall trial begins when the first subject signs the informed consent form. The overall trial ends when the last subject completes the last trial visit, discontinues from the trial or is lost to follow-up (i.e. the subject is unable to be contacted by the investigator). Upon study completion, subjects are discontinued and enrolled in a pembrolizumab extension trial.

5.11 Clinical Criteria for Early Trial Termination

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

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

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

6.0 TRIAL FLOW CHART

6.1 Pembrolizumab Arm: Treatment and Follow-up Phase

	Screening (Visit 1)	Treatment Cycles[1]													End of Treatment Phase		Observation Phase[22] (pre-PD)	Follow up Phase[24]			Survival Follow up[27]
Treatment Cycle / Scheduled Time	-42 to -1	1	2	3	4	5	6	7	8	9	10	11	12	13 and Beyond	Discontinuation Visit[20]	Safety Follow up Visit[21]	Observation Visit	Follow up Visit 1	Follow up Visit 2	Follow up Visit 3 and Beyond	Survival Follow up Visit 1 and Beyond
Scheduling Window (Days):[2]		± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	At Study Drug Discontinuation +/- 3	30 days from Last Dose +/- 3	± 3	3 Months from Last Dose +/- 7	6 Months from Last Dose +/- 7	Every 3 Months after Visit 2+/- 7	Approx. Every 2 Months +/- 14
Administrative Procedures																					
Informed Consent	X																				
Informed Consent for Future Biomedical Research (optional)	X																				
Inclusion/Exclusion Criteria	X																				
Subject ID Card	X																				
Demographics and Medical History	X																				
Review Prior and Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
NSCLC Disease Details and Prior Treatment	X																				

	Screening (Visit 1)	Treatment Cycles[1]													End of Treatment Phase		Observation Phase[22] (pre-PD)	Follow up Phase[24]			Survival Follow up[27]
Treatment Cycle / Scheduled Time	-42 to -1	1	2	3	4	5	6	7	8	9	10	11	12	13 and Beyond	Discontinuation Visit[20]	Safety Follow up Visit[21]	Observation Visit	Follow up Visit 1	Follow up Visit 2	Follow up Visit 3 and Beyond	Survival Follow up Visit 1 and Beyond
Scheduling Window (Days):[2]		± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	At Study Drug Discontinuation +/- 3	30 days from Last Dose +/- 3	± 3	3 Months from Last Dose +/- 7	6 Months from Last Dose +/- 7	Every 3 Months after Visit 2+/- 7	Approx. Every 2 Months +/- 14
Subsequent antineoplastic therapy status															X	X	X	X	X	X	X
Survival Status[27]		< ---------->																			X
Clinical Procedures / Assessments																					
Review Adverse Events[25]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Full Physical Examination	X														X						
Directed Physical Examination		X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X		
Vital Signs and Weight [14]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
12-Lead ECG	X																				
ECOG Performance Status	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
EuroQol EQ-5D [18]		X	X	X			X			X			X	X	X	X	X				
EORTC QLQ-C30 [18]		X	X	X			X			X			X	X	X	X	X				
EORTC QLQ LC-13 [18]		X	X	X			X			X			X	X	X	X	X				

	Screening (Visit 1)	Treatment Cycles[1]													End of Treatment Phase		Observation Phase[22] (pre-PD)	Follow up Phase[24]			Survival Follow up[27]
Treatment Cycle / Scheduled Time	-42 to -1	1	2	3	4	5	6	7	8	9	10	11	12	13 and Beyond	Discontinuation Visit[20]	Safety Follow up Visit[21]	Observation Visit	Follow up Visit 1	Follow up Visit 2	Follow up Visit 3 and Beyond	Survival Follow up Visit 1 and Beyond
Scheduling Window (Days):[2]		± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	At Study Drug Discontinuation +/- 3	30 days from Last Dose +/- 3	± 3	3 Months from Last Dose +/- 7	6 Months from Last Dose +/- 7	Every 3 Months after Visit 2+/- 7	Approx. Every 2 Months +/- 14
Oncology Health Economic Assessment (HEA)[19]			X	X	X	X	X	X	X		X		X	X	X	X	X				
Central Laboratory Procedures/Assessments																					
Blood for Future Biomedical Research (optional)[11]		X																			
Pharmacokinetics[15]		X	X		X				X					X		X		X	X		
Anti-pembrolizumab Antibodies[16]		X	X		X				X					X		X		X	X		
Blood for Genetics[13]		X																			
Study Drug Administration																					
Pembrolizumab[10]		X	X	X	X	X	X	X	X	X	X	X	X	X							
Local Laboratory Procedures / Assessments																					
Pregnancy Test - Urine or Serum β-HCG[3]	X																				

	Screening (Visit 1)	Treatment Cycles[1]													End of Treatment Phase		Observation Phase[22] (pre-PD)	Follow up Phase[24]			Survival Follow up[27]
Treatment Cycle / Scheduled Time	-42 to -1	1	2	3	4	5	6	7	8	9	10	11	12	13 and Beyond	Discontinuation Visit[20]	Safety Follow up Visit[21]	Observation Visit	Follow up Visit 1	Follow up Visit 2	Follow up Visit 3 and Beyond	Survival Follow up Visit 1 and Beyond
Scheduling Window (Days):[2]		± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	At Study Drug Discontinuation +/- 3	30 days from Last Dose +/- 3	± 3	3 Months from Last Dose +/- 7	6 Months from Last Dose +/- 7	Every 3 Months after Visit 2+/- 7	Approx. Every 2 Months +/- 14
PT/INR and aPTT[4]	X[5]																				
CBC with Differential[17]	X[5]		X	X	X	X	X	X	X	X	X		X	X	X	X	X[23]				
Comprehensive Chemistry Panel[17]	X[5]		X	X	X	X	X	X	X	X	X		X	X	X	X	X[23]				
Urinalysis[6]	X[5]					X				X				X	X	X	X[23]				
T3,FT4 and TSH[7]	X[5]		X		X		X		X		X		X	X	X	X	X[23]				
ALK Translocation Testing[9]	X																				
EGFR Mutation Testing[9]	X																				
Efficacy Measurements																					
Tumor Imaging[8]	X			X			X			X			X	X	X	X	X	X[26]	X[26]	X[26]	
Brain Imaging[28]	X																				

	Screening (Visit 1)	Treatment Cycles[1]													End of Treatment Phase		Observation Phase[22] (pre-PD)	Follow up Phase[24]			Survival Follow up[27]
Treatment Cycle / Scheduled Time	-42 to -1	1	2	3	4	5	6	7	8	9	10	11	12	13 and Beyond	Discontinuation Visit[20]	Safety Follow up Visit[21]	Observation Visit	Follow up Visit 1	Follow up Visit 2	Follow up Visit 3 and Beyond	Survival Follow up Visit 1 and Beyond
Scheduling Window (Days):[2]		± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	At Study Drug Discontinuation +/- 3	30 days from Last Dose +/- 3	± 3	3 Months from Last Dose +/- 7	6 Months from Last Dose +/- 7	Every 3 Months after Visit 2+/- 7	Approx. Every 2 Months +/- 14
Tumor Biopsies / Archival Tissue Collection																					
Tumor tissue collection for PD-L1 expression [12]	X																				

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

2 In general, the window for each visit is +/- 3 days unless otherwise specified.

3 For women of reproductive potential, a urine pregnancy test will be performed within 72 hours prior to first dose of trial treatment. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test, performed by the local study site laboratory, will be required. Pregnancy tests (serum and/or urine tests) should be repeated if required by local guidelines.

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

5 Laboratory tests for screening are to be performed within 10 days prior to the first dose of trial treatment. See Section 7.1.3 for details regarding laboratory tests.

6 After Cycle 1, lab samples can be collected up to 48 hours prior to the scheduled time point. Laboratory results must be known and acceptable prior to dosing. See Section 7.1.3 for details regarding laboratory tests. Perform every 4 cycles after Cycle 13.

7 Thyroid function tests will be performed by a central laboratory only if the local laboratory is unable to perform this service. After Cycle 1, lab samples can be collected up to 48 hours prior to the scheduled time point. Laboratory results must be known and acceptable prior to dosing. See Section 7.1.3 for details regarding laboratory tests. Performed every 2 cycles after Cycle 13.

8 Sponsor will collect radiological assessments for analysis by a central vendor. The initial tumor imaging will be performed within 30 days prior to randomization. Scans performed as part of routine clinical management are acceptable for use as the screening scan if they are of diagnostic quality. On study imaging will be performed every 9 weeks (63 ± 7 days) calculated from the randomization date or more frequently if clinically indicated and submitted for central radiology review. The timing for imaging studies should follow calendar days and should not be adjusted for delays in cycle starts. The same imaging technique should be used in a subject throughout the trial. Imaging assessments should be performed every 9 weeks (+/- 7 days from randomization. Additional imaging at Discontinuation Visit and Safety Follow-up Visit is not required provided that imaging assessments have been performed per schedule. Imaging will continue at the protocol defined interval until the time of PD, pregnancy, or the start of a new cancer treatment

9 Site must be able to provide documentation of the subject's tumor EGFR mutation and/or ALK translocation mutation status in patients with non-squamous histologies OR if clinically indicated. If the site is unable to provide this source documentation, or site level testing, then the Sponsor will offer this molecular testing of the tumor.

10 Pembrolizumab can be administered for up to 35 treatments.

11 Informed consent for Future Biomedical Research (FBR) samples must be obtained before the DNA sample is drawn. DNA sample for analysis should be obtained predose, on Cycle 1 (or with the next scheduled blood draw), as the last sample drawn, on allocated subjects only, or at a later date as soon as the informed consent is obtained. This sample should only be taken once from each subject. See Section 12.2 for guidance regarding the collection and management of specimens for FBR.

12 Tumor tissue for biomarker analysis from a biopsy of a tumor lesion not previously irradiated must be provided. Only biopsies obtained at the time of or after the diagnosis of metastatic disease will be

	Screening (Visit 1)	Treatment Cycles[1]													End of Treatment Phase		Observation Phase[22] (pre-PD)	Follow up Phase[24]			Survival Follow up[27]
Treatment Cycle / Scheduled Time	-42 to -1	1	2	3	4	5	6	7	8	9	10	11	12	13 and Beyond	Discontinuation Visit[20]	Safety Follow up Visit[21]	Observation Visit	Follow up Visit 1	Follow up Visit 2	Follow up Visit 3 and Be-yond	Survival Follow up Visit 1 and Beyond
Scheduling Window (Days):[2]		± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	At Study Drug Discontinuation +/- 3	30 days from Last Dose +/- 3	± 3	3 Months from Last Dose +/- 7	6 Months from Last Dose +/- 7	Every 3 Months after Visit 2+/- 7	Approx. Every 2 Months +/- 14

evaluated for PD-L1 expression. Any leftover tumor tissue will be stored for future research if the subject signs the optional FBR consent. If a tumor biopsy was obtained from a target lesion during eligibility assessment, it is preferred to obtain a new baseline scan. Biopsy of lesions on study should be limited to non-target lesions or new lesions if their pathologic etiology is ambiguous.

13 Blood for genetics sample will be collected to explore host genetics and to identify genetic predictors which may have a role in therapeutic response to pembrolizumab. This sample should be drawn for planned, exploratory genetic analysis of DNA unless there is either a documented law or regulation prohibiting collection, or unless the IRB/IEC does not approve of the collection.

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

15 Pre-dose (trough) samples at cycle 1, 2, 4, 8 and every 8 cycles thereafter while the subject is receiving pembrolizumab. Once the subject discontinues taking pembrolizumab additional samples should be obtained at 1, 3 and 6 months after last dose of study medication. All trough samples should be drawn within 24 hours before infusion of pembrolizumab and at the same time as blood collection for anti-pembrolizumab antibodies. Post-dose samples at cycle 1 should be drawn within 30 minutes after end of infusion, and one sample between 72 and 168 hr post-infusion.

16 Pre-dose (trough) samples at cycle 1, 2, 4, 8 and every 8 cycles thereafter while the subject is receiving pembrolizumab. Once the subject discontinues taking pembrolizumab additional samples should be obtained at 1, 3 and 6 months after last dose of study medication. All trough samples should be drawn within 24 hours before infusion of pembrolizumab.

17 After Cycle 1, lab samples can be collected up to 48 hours prior to the scheduled time point. Laboratory results must be known and acceptable prior to dosing. See Section 7.1.3 for details regarding laboratory tests. CBC and chemistry will be performed every cycle up to cycle 10, then every other cycle thereafter.

18 PROs are assessed every cycle for the first three cycles and every third cycle (every 9 weeks) thereafter until PD while the subject is receiving study treatment. PROs will also be obtained at the Treatment Discontinuation Visit and 30-day Safety Follow-up Visit. If the Treatment Discontinuation Visit occurs 30 days from the last dose of study treatment, at the time of the mandatory Safety Follow up Visit, PROs do not need to be repeated. During the Observation phase, PROs should continue to be assessed every 9 weeks until PD. PROs are to be administered by trained site personnel and completed electronically by subjects prior to all other study procedures and receiving results of any tests (including disease status). The PROs should be administered in the following order: EuroQol EQ-5D followed by EORTC QLQ-C30 and then EORTC QLQ-LC13.

19 The Oncology HEA will be completed every cycle between cycles 2 to 8 and then every other cycle thereafter until PD while the subject is receiving study treatment. The Oncology HEA will also be obtained at the Treatment Discontinuation Visit and 30-day Safety Follow-up Visit. If the Treatment Discontinuation Visit occurs 30 days from the last dose of study treatment, at the time of the mandatory Safety Follow up Visit, the HEA does not need to be repeated. During the Observation phase, the HEA should continue to be assessed every 6 weeks until PD. The Oncology HEA will be administered and completed by qualified site personnel after the subject completes all other questionnaires and prior to all other study procedures.

20 The Discontinuation Visit should occur at the time study drug is discontinued for any reason. If the Discontinuation Visit occurs 30 days from the last dose of study treatment, at the time of the mandatory Safety Follow up Visit, procedures do not need to be repeated. Imaging assessments should be performed every 9 weeks (+/- 7 days from randomization. Additional imaging at Discontinuation Visit and Safety Follow-up Visit is not required provided that imaging assessments have been performed per schedule. Imaging will continue at the protocol defined interval until the time of PD, pregnancy, or the start of a new cancer treatment

21 The mandatory Safety Follow-up Visit for all subjects should be conducted approximately 30 days after the last dose of trial treatment or before the initiation of new antineoplastic treatment, whichever comes first. Subjects with an AE of Grade >1 will be further followed until the resolution of the AE to Grade 0-1 or until beginning of a new antineoplastic therapy, whichever occurs first. Subjects who are eligible for treatment with pembrolizumab during the Second Course Phase may have up to three Safety Follow-up Visits, one after the Treatment Phase, Crossover Phase and the Second Course Phase. If the Discontinuation Visit occurs approximately 30 days (+/- 3 days) from last dose trial treatment the same procedures do not need to be repeated for the Safety Follow-up Visit. Imaging assessments should be performed every 9 weeks (+/- 7 days from randomization. Additional imaging at Discontinuation Visit and Safety Follow-up Visit is not required provided that imaging assessments have been performed per schedule. Imaging will continue at the protocol defined interval until the time of PD, pregnancy, or the start of a new cancer treatment

22 The Observation Phase is for any subject that discontinued study treatment for reasons other than pregnancy or PD (i.e., toxicity). Pembrolizumab subjects remain in the Observation Phase until the

	Screening (Visit 1)	Treatment Cycles[1]													End of Treatment Phase		Observation Phase[22] (pre-PD)	Follow up Phase[24]			Survival Follow up[27]
Treatment Cycle / Scheduled Time	-42 to -1	1	2	3	4	5	6	7	8	9	10	11	12	13 and Beyond	Discontinuation Visit[20]	Safety Follow up Visit[21]	Observation Visit	Follow up Visit 1	Follow up Visit 2	Follow up Visit 3 and Beyond	Survival Follow up Visit 1 and Beyond
Scheduling Window (Days):[2]		± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	At Study Drug Discontinuation +/- 3	30 days from Last Dose +/- 3	± 3	3 Months from Last Dose +/- 7	6 Months from Last Dose +/- 7	Every 3 Months after Visit 2+/- 7	Approx. Every 2 Months +/- 14

time of PD, pregnancy, or the start of a new antineoplastic therapy. Observation visits should begin 4 weeks (28 days +/- 7 days) from the Safety Follow-up Visit and follow a Q3W (21 days +/- 3 days) schedule thereafter. Tumor imaging for the Observation Visits should be maintained Q9W by following the same calendar day schedule that was initiated during Treatment Cycles. For subjects who have received at least 15 treatment cycles of pembrolizumab, the frequency of tumor imaging may be reduced to every 12 weeks (84 +/- 7 days) during the Observation Visits.

23 During the Observation Phase, these laboratory assessments should be obtained every 12 weeks.

24 Subjects who stop pembrolizumab after 35 trial treatments and have achieved PR and/or SD OR have achieved CR (see section 7.1.5.5) will move to the Follow up Phase of the study. Follow up visit 1 should take place 3 months after the last dose of trial treatment. Follow up visit 2 should take place 6 months after last dose of trial treatment and additional Follow up visits should take place every 3 months thereafter. Subjects who experience disease progression (and do not continue into the Second Course Phase) or start a new antineoplastic therapy will move directly into Survival Follow up. For subject convenience, all Follow up assessments may occur during the same visit as the imaging studies are obtained. Subjects with an AE of Grade >1 will be further followed until the resolution of the AE to Grade 0-1 or until beginning of a new antineoplastic therapy, whichever occurs first.

25 Once a subject discontinues study treatment, report all SAEs (related and unrelated to trial treatment), ECIs, and irAEs occurring within 90 days following cessation of treatment or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier. After this time, report only SAEs and ECIs that are considered related to trial treatment.

26 Tumor imaging is not needed for subjects who start another anti-cancer treatment regimen.

27 Once the subject stops the imaging assessments for this protocol (e.g. for PD or starting a new antineoplastic therapy), the subject moves into the Survival Follow-up Phase and should be contacted by telephone approximately every 2 months to assess for survival status. Post-study treatments and the subject's response to them will also be collected. Updated survival status may be requested by the Sponsor at any time during the course of the study. Upon Sponsor notification, all subjects who do not/will not have a scheduled study visit or study contact during the Sponsor-defined time period will be contacted for their survival status (excluding subjects who have a death event previously recorded).

28 See Brain Imaging in Section 7.1.2.7 and the Site Imaging Manual for acceptable imaging modalities

6.2 SOC Arm: Treatment and Follow-up Phase

	Screening (Visit 1)	Treatment Cycles[1]													End of Treatment Phase		Observation Phase[20] (pre-PD)	Survival Follow up[23]
Treatment Cycle / Scheduled Time	-42 to -1	1	2	3	4	5	6	7	8	9	10	11	12	13 and Beyond	Discontinuation Visit[18]	Safety Follow Up Visit[19]	Observation Visit	Survival Follow up Visit 1 and Beyond
Scheduling Window (Days):[2]		± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	At Study Drug Discontinuation +/- 3	30 Days from Last Dose +/- 3	± 3	Approx. Every 2 Months +/- 14
Administrative Procedures																		
Informed Consent	X																	
Informed Consent for Future Biomedical Research (optional)	X																	
Inclusion/Exclusion Criteria	X																	
Subject ID Card	X																	
Demographics and Medical History	X																	
Review Prior and Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
NSCLC Disease Details and Prior Treatment	X																	
Subsequent antineoplastic therapy status															X	X	X	X
Survival Status[23]		< ----------																X
Clinical Procedures / Assessments																		
Review Adverse Events[22]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Full Physical Examination	X														X			
Directed Physical Examination		X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	
Vital Signs and Weight [14]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

	Screening (Visit 1)	Treatment Cycles[1]													End of Treatment Phase		Observation Phase[20] (pre-PD)	Survival Follow up[23]
Treatment Cycle / Scheduled Time	-42 to -1	1	2	3	4	5	6	7	8	9	10	11	12	13 and Beyond	Discontinuation Visit[18]	Safety Follow Up Visit[19]	Observation Visit	Survival Follow up Visit 1 and Beyond
Scheduling Window (Days):[2]		± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	At Study Drug Discontinuation +/- 3	30 Days from Last Dose +/- 3	± 3	Approx. Every 2 Months +/- 14
12-Lead ECG	X																	
ECOG Performance Status	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
EuroQol EQ-5D[16]		X	X	X			X			X			X	X	X	X	X	
EORTC QLQ-C30[16]		X	X	X			X			X			X	X	X	X	X	
EORTC QLQ QLQ-LC13[16]		X	X	X			X			X			X	X	X	X	X	
Oncology Health Economic Assessment (HEA)[17]			X	X	X	X	X	X	X		X		X	X	X	X	X	
Central Laboratory Procedures/Assessments																		
Blood for Future Biomedical Research (optional)[11]		X																
Blood for Genetics[13]		X																
Study Drug Administration																		
Carboplatin/Pemetrexed[10]		X	X	X	X	X	X	X	X	X	X	X	X	X				
Cisplatin/Pemetrexed[10]		X	X	X	X	X	X	X	X	X	X	X	X	X				
Paclitaxel/Carboplatin[10]		X	X	X	X	X	X	X	X	X	X	X	X	X				
Carboplatin/Gemcitabine		X	X	X	X	X	X											
Cisplatin/Gemcitabine		X	X	X	X	X	X											

	Screening (Visit 1)	Treatment Cycles[1]												End of Treatment Phase		Observation Phase[20] (pre-PD)	Survival Follow up[23]
Treatment Cycle / Scheduled Time	-42 to -1	1	2	3	4	5	6	7	8	9	10	11	12	13 and Beyond	Discontinuation Visit[18]	Safety Follow Up Visit[19]	Observation Visit	Survival Follow up Visit 1 and Beyond
Scheduling Window (Days):[2]		± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	At Study Drug Discontinuation +/- 3	30 Days from Last Dose +/- 3	± 3	Approx. Every 2 Months +/- 14
Local Laboratory Procedures / Assessments																		
Pregnancy Test - Urine or Serum β-HCG[3]	X																	
PT/INR and aPTT[4]	X[5]																	
CBC with Differential[15]	X[5]		X	X	X	X	X	X	X	X	X		X	X	X	X	X[21]	
Comprehensive Chemistry Panel[15]	X[5]		X	X	X	X	X	X	X	X	X		X	X	X	X	X[21]	
Urinalysis[6]	X[5]					X				X				X	X	X	X[21]	
T3,FT4 and TSH[7]	X[5]		X		X		X		X		X		X	X	X	X	X[21]	
ALK Translocation Testing[9]	X																	
EGFR Mutation Testing[9]	X																	
Efficacy Measurements																		
Tumor Imaging[8]	X			X			X			X			X	X	X	X	X	
Brain Imaging[24]	X																	
Tumor Biopsies / Archival Tissue Collection																		
Tumor tissue collection for PD-L1 expression[12]	X																	

	Screening (Visit 1)	Treatment Cycles[1]													End of Treatment Phase		Observation Phase[20] (pre-PD)	Survival Follow up[23]
Treatment Cycle / Scheduled Time	-42 to -1	1	2	3	4	5	6	7	8	9	10	11	12	13 and Beyond	Discontinuation Visit[18]	Safety Follow Up Visit[19]	Observation Visit	Survival Follow up Visit 1 and Beyond
Scheduling Window (Days):[2]		± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	At Study Drug Discontinuation +/- 3	30 Days from Last Dose +/- 3	± 3	Approx. Every 2 Months +/- 14

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

2 In general, the window for each visit is +/- 3 days unless otherwise specified.

3 For women of reproductive potential, a urine pregnancy test will be performed within 72 hours prior to first dose of trial treatment. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test, performed by the local study site laboratory, will be required. Pregnancy tests (serum and/or urine tests) should be repeated if required by local guidelines.

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

5 Laboratory tests for screening are to be performed within 10 days prior to the first dose of trial treatment. See Section 7.1.3 for details regarding laboratory tests.

6 After Cycle 1, lab samples can be collected up to 48 hours prior to the scheduled time point. Laboratory results must be known and acceptable prior to dosing. See Section 7.1.3 for details regarding laboratory tests. Perform every 4 cycles after Cycle 13.

7 Thyroid function tests will be performed by a central laboratory only if the local laboratory is unable to perform this service. After Cycle 1, lab samples can be collected up to 48 hours prior to the scheduled time point. Laboratory results must be known and acceptable prior to dosing. See Section 7.1.3 for details regarding laboratory tests. Performed every 2 cycles after Cycle 13.

8 Sponsor will collect radiological assessments for analysis by a central vendor. The initial tumor imaging will be performed within 30 days prior to randomization. Scans performed as part of routine clinical management are acceptable for use as the screening scan if they are of diagnostic quality. On study imaging will be performed every 9 weeks (63 ± 7 days) calculated from the randomization date or more frequently if clinically indicated and submitted for central radiology review. The timing for imaging studies should follow calendar days and should not be adjusted for delays in cycle starts. The same imaging technique should be used in a subject throughout the trial. Imaging assessments should be performed every 9 weeks (+/- 7 days from randomization. Additional imaging at Discontinuation Visit and Safety Follow-up Visit is not required provided that imaging assessments have been performed per schedule. Imaging will continue at the protocol defined interval until the time of PD, pregnancy, or the start of a new cancer treatment

9 Site must be able to provide documentation of the subject's tumor EGFR mutation and/or ALK translocation mutation status in patients with non-squamous histologies OR if clinically indicated. If the site is unable to provide this source documentation, or site level testing, then the Sponsor will offer this molecular testing of the tumor.

10 This regimen to be administered up to a maximum of 6 cycles. Pemetrexed may be given after 4 cycles of Carboplatin/Pemetrexed, Cisplatin/Pemetrexed or Paclitaxel/Carboplatin in subjects with non-squamous histologies.

11 Informed consent for Future Biomedical Research (FBR) samples must be obtained before the DNA sample is drawn. DNA sample for analysis should be obtained predose, on Cycle 1 (or with the next scheduled blood draw), as the last sample drawn, on allocated subjects only, or at a later date as soon as the informed consent is obtained. This sample should only be taken once from each subject. See Section 12.2 for guidance regarding the collection and management of specimens for FBR.

12 Tumor tissue for biomarker analysis from a biopsy of a tumor lesion not previously irradiated must be provided. Only biopsies obtained at the time of or after the diagnosis of metastatic disease will be evaluated for PD-L1 expression. Any leftover tumor tissue will be stored for future research if the subject signs the optional FBR consent. If a tumor biopsy was obtained from a target lesion during eligibility assessment, it is preferred to obtain a new baseline scan. Biopsy of lesions on study should be limited to non-target lesions or new lesions if their pathologic etiology is ambiguous.

13 Blood for genetics sample will be collected to explore host genetics and to identify genetic predictors which may have a role in therapeutic response to pembrolizumab. This sample should be drawn for planned, exploratory genetic analysis of DNA unless there is either a documented law or regulation prohibiting collection, or unless the IRB/IEC does not approve of the collection.

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

15 After Cycle 1, lab samples can be collected up to 48 hours prior to the scheduled time point. Laboratory results must be known and acceptable prior to dosing. See Section 7.1.3 for details regarding laboratory tests. CBC and chemistry will be performed every cycle up to cycle 10, then every other cycle thereafter. Additional laboratory assessments required for the SOC platinum doublets offered in this trial, but not included in the above Flowchart, should be obtained per local guidance and results recorded in the appropriate CRF.

16 PROs are assessed every cycle for the first three cycles and every third cycle (every 9 weeks) thereafter until PD while the subject is receiving study treatment. PROs will also be obtained at the Treatment Discontinuation Visit and 30-day Safety Follow-up Visit. If the Treatment Discontinuation Visit occurs 30 days from the last dose of study treatment, at the time of the mandatory Safety Follow up Visit, PROs do not need to be repeated. During the Observation phase, PROs should continue to be assessed every 9 weeks until PD. PROs are to be administered by trained site

	Screening (Visit 1)	Treatment Cycles[1]													End of Treatment Phase		Observation Phase[20] (pre-PD)	Survival Follow up[23]
Treatment Cycle / Scheduled Time	-42 to -1	1	2	3	4	5	6	7	8	9	10	11	12	13 and Beyond	Discontinuation Visit[18]	Safety Follow Up Visit[19]	Observation Visit	Survival Follow up Visit 1 and Beyond
Scheduling Window (Days):[2]		± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	At Study Drug Discontinuation +/- 3	30 Days from Last Dose +/- 3	± 3	Approx. Every 2 Months +/- 14

personnel and completed electronically by subjects prior to all other study procedures and receiving results of any tests (including disease status). The PROs should be administered in the following order: EuroQol EQ-5D followed by EORTC QLQ-C30 and then EORTC QLQ-LC13.

17 The Oncology HEA will be completed every cycle between cycles 2 to 8 and then every other cycle thereafter until PD while the subject is receiving study treatment. The Oncology HEA will also be obtained at the Treatment Discontinuation Visit and 30-day Safety Follow-up Visit. If the Treatment Discontinuation Visit occurs 30 days from the last dose of study treatment, at the time of the mandatory Safety Follow up Visit, the HEA does not need to be repeated. During the Observation phase, the HEA should continue to be assessed every 6 weeks until PD. The Oncology HEA will be administered and completed by qualified site personnel after the subject completes all other questionnaires and prior to all other study procedures.

18 The Discontinuation Visit should occur at the time study drug is discontinued for any reason. If the Discontinuation Visit occurs 30 days from the last dose of study treatment, at the time of the mandatory Safety Follow up Visit, procedures do not need to be repeated. Imaging assessments should be performed every 9 weeks (+/- 7 days from randomization. Additional imaging at Discontinuation Visit and Safety Follow-up Visit is not required provided that imaging assessments have been performed per schedule. Imaging will continue at the protocol defined interval until the time of PD, pregnancy, or the start of a new cancer treatment

19 The mandatory Safety Follow-up Visit for all subjects should be conducted approximately 30 days after the last dose of trial treatment or before the initiation of new antineoplastic treatment, whichever comes first. Subjects with an AE of Grade >1 will be further followed until the resolution of the AE to Grade 0-1 or until beginning of a new antineoplastic therapy, whichever occurs first. Subjects who are eligible for treatment with pembrolizumab during the Second Course Phase may have up to three Safety Follow-up Visits, one after the Treatment Phase, Crossover Phase and the Second Course Phase. If the Discontinuation Visit occurs approximately 30 days (+/- 3 days) from last dose trial treatment the same procedures do not need to be repeated for the Safety Follow-up Visit. Imaging assessments should be performed every 9 weeks (+/- 7 days from randomization. Additional imaging at Discontinuation Visit and Safety Follow-up Visit is not required provided that imaging assessments have been performed per schedule. Imaging will continue at the protocol defined interval until the time of PD, pregnancy, or the start of a new cancer treatment

20 The Observation Phase is for any subject that discontinued study treatment for reasons other than pregnancy or PD (i.e., toxicity). Observation visits should begin 4 weeks (28 days +/- 7 days) from the Safety Follow-up Visit and follow a Q3W (21 days +/- 3 days) schedule thereafter. Tumor imaging for the Observation Visits should be maintained Q9W by following the same calendar day schedule that was initiated during Treatment Cycles.

21 During the Observation Phase, these laboratory assessments should be obtained every 12 weeks.

22 Once a subject discontinues study treatment, report all SAEs (related and unrelated to trial treatment), ECIs, and irAEs occurring within 90 days following cessation of treatment or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier. After this time, report only SAEs and ECIs that are considered related to trial treatment.

23 Once the subject stops the imaging assessments for this protocol (e.g. for PD or starting a new antineoplastic therapy), the subject moves into the Survival Follow-up Phase and should be contacted by telephone approximately every 2 months to assess for survival status. Post-study treatments and the subject's response to them will also be collected. Updated survival status may be requested by the Sponsor at any time during the course of the study. Upon Sponsor notification, all subjects who do not/will not have a scheduled study visit or study contact during the Sponsor-defined time period will be contacted for their survival status (excluding subjects who have a death event previously recorded).

24 See Brain Imaging in Section 7.1.2.7 and the Site Imaging Manual for acceptable imaging modalities

6.3 Second Course Treatment and Follow-up Phase

	Second Course Treatment Cycles[1]													End of Second Course Treatment		Follow up Phase[14]			Survival Follow up[10]
Treatment Cycle / Scheduled Time	1	2	3	4	5	6	7	8	9	10	11	12	13	Discontinuation Visit	Safety Follow up Visit[13]	Follow up Visit 1	Follow up Visit 2	Follow up Visit 3 and beyond	Survival Follow up Visit 1 and beyond
Scheduling Window (Days):[2]		±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	At Study Drug Discontinuation +/- 3	30 Days from Last Dose +/- 3	3 Months from Last Dose +/- 7	6 Months from Last Dose +/- 7	Every 3 Months after Visit 2 +/- 7	Approx. Every 2 Months +/- 14
Administrative Procedures																			
Eligibility Criteria	X																		
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Subsequent antineoplastic therapy status															X	X	X	X	X
Survival status[10]	<----------																		----------> X
Study Drug Administration																			
Pembrolizumab[12]	X	X	X	X	X	X	X	X	X	X	X	X	X						
Clinical Procedures / Assessments																			
Review Adverse Events[11]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Full Physical Examination	X													X					
Directed Physical Examination		X	X	X	X	X	X	X	X	X	X	X	X		X	X	X		
Vital Signs and Weight[15]	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		

	Second Course Treatment Cycles[1]													End of Second Course Treatment		Follow up Phase[14]			Survival Follow up[10]
Treatment Cycle / Scheduled Time	1	2	3	4	5	6	7	8	9	10	11	12	13	Discontinuation Visit	Safety Follow up Visit[13]	Follow up Visit 1	Follow up Visit 2	Follow up Visit 3 and beyond	Survival Follow up Visit 1 and beyond
Scheduling Window (Days):[2]		±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	At Study Drug Discontinuation +/- 3	30 Days from Last Dose +/- 3	3 Months from Last Dose +/- 7	6 Months from Last Dose +/- 7	Every 3 Months after Visit 2 +/- 7	Approx. Every 2 Months +/- 14
Pregnancy Test - Urine or Serum β-HCG[3, 5]	X																		
PT/INR and aPTT[4, 5]	X																		
CBC with Differential[5, 9]	X	X	X	X	X	X	X	X	X	X		X		X	X[16]	X[16]	X[16]		
Comprehensive Chemistry Panel[5 9]	X	X	X	X	X	X	X	X	X	X		X		X	X[16]	X[16]	X[16]		
Urinalysis[5, 6]	X				X				X				X	X	X[16]				
T3, FT4 and TSH[5,7]	X		X		X		X		X		X		X	X	X[16]	X[16]	X[16]		
Efficacy Measurements																			
Tumor Imaging[8]	X			X			X			X			X	X	X	X	X	X	

1 In general, assessments/procedures are to be performed on Day 1 and prior to the first dose of trial treatment for each cycle unless otherwise specified. Treatment cycles are 3 weeks (21- days). If treatment cycles are adjusted all procedures except imaging will be completed according to the Cycle number and not weeks on therapy.

2 In general, the window for each visit is +/- 3 days unless otherwise specified.

3 For women of reproductive potential, a urine pregnancy test will be performed within 72 hours prior to the first Second Course dose. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test, performed by the local study site laboratory, will be required. Pregnancy tests (serum and/or urine tests) should be repeated if required by local guidelines.

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

5 Laboratory tests for determining eligibility for Second Course Phase are to be performed within 10 days prior to the first dose of pembrolizumab. See Section 7.1.3 for details regarding laboratory tests.

6 After the first dose, lab samples can be collected up to 48 hours prior to the scheduled time point. Laboratory results must be known and acceptable prior to dosing. See Section 7.1.3 for details regarding laboratory tests. Perform every 4 cycles after cycle 13.

7 After the first dose, lab samples can be collected up to 48 hours prior to the scheduled time point. Laboratory results must be known and acceptable prior to dosing. See Section 7.1.3 for details regarding laboratory tests. Thyroid function tests will be performed by a central laboratory only if the local laboratory is unable to perform this service. Thyroid function tests should be performed every other cycle.

8 Sponsor will collect radiological assessments for analysis by a central vendor. If the subject enters the Second Course Phase, Cycle 1 scan may be performed up to 30 days prior to the first dose of trial treatment in the Second Course Phase. Imaging will be performed every 9 weeks (63 +/-7 days) after the first dose of Second Course Phase trial treatment up until cycle 13 and every 12 weeks (84 +/- 7 days) thereafter. The timing of imaging should follow calendar days and should not be adjusted for delays in cycle starts. The same imaging technique should be used in a subject throughout the

	Second Course Treatment Cycles[1]													End of Second Course Treatment		Follow up Phase[14]			Survival Follow up[10]
Treatment Cycle / Scheduled Time	1	2	3	4	5	6	7	8	9	10	11	12	13	Discontinuation Visit	Safety Follow up Visit[13]	Follow up Visit 1	Follow up Visit 2	Follow up Visit 3 and beyond	Survival Follow up Visit 1 and beyond
Scheduling Window (Days):[2]		±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	At Study Drug Discontinuation +/- 3	30 Days from Last Dose +/- 3	3 Months from Last Dose +/- 7	6 Months from Last Dose +/- 7	Every 3 Months after Visit 2 +/- 7	Approx. Every 2 Months +/- 14

trial. Subjects who discontinue trial treatment due to reasons other than disease progression, should continue to be assessed every 9 weeks (63 +/- 7 days) by radiologic imaging until the start of a new antineoplastic therapy, documented disease progression, or death, whichever occurs first. If trial treatment is discontinued after cycle 13, tumor imaging should be performed every 12 weeks (84 days +/- 7 days). Continued imaging is not needed for subjects who start another antineoplastic treatment. The same imaging technique should be used in a subject throughout the trial. Imaging assessments should be performed every 9 weeks (+/- 7 days from randomization. Additional imaging at Discontinuation Visit and Safety Follow-up Visit is not required provided that imaging assessments have been performed per schedule. Imaging will continue at the protocol defined interval until the time of PD, pregnancy, or the start of a new cancer treatment

9 After the first dose, lab samples can be collected up to 48 hours prior to the scheduled time point. Laboratory results must be known and acceptable prior to dosing. See Section 7.1.3 for details regarding laboratory tests. CBC and chemistry will be performed every cycle up to cycle 10, then every other cycle thereafter.

10 Once a subject experiences disease progression or starts a new antineoplastic therapy, the subject moves into the Survival Follow-up Phase and should be contacted by telephone approximately every 2 months to assess for survival status and start of new antineoplastic therapy if applicable. Updated survival status may be requested by the Sponsor at any time during the course of the study. Upon Sponsor notification, all subjects who do not/will not have a scheduled study visit or study contact during the Sponsor-defined time period will be contacted for their survival status (excluding subjects who have a death event previously recorded).

11 Record all AEs occurring within 30 days after the last dose of trial treatment. Report all SAEs (related and unrelated to trial treatment), ECIs, and irAEs occurring within 90 days following cessation of treatment or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier. After this time, report only SAEs and ECIs that are considered related to trial treatment.

12 Pembrolizumab can be administered up to 17 trial treatment in Second Course Phase.

13 The mandatory Safety Follow-Up Visit should be conducted approximately 30 days after the last dose of trial treatment or before the initiation of a new antineoplastic treatment, whichever comes first. Subjects with an AE of Grade >1 will be further followed until the resolution of the AE to Grade 0-1 or until beginning of a new antineoplastic therapy, whichever occurs first. Subjects who are eligible per the requirements in Section 7.1.5.5 for treatment with pembrolizumab during the Second Course Phase may have up to three Safety Follow-up Visits, one after the Treatment Phase, Crossover Phase and the Second Course Phase. Imaging assessments should be performed every 9 weeks (+/- 7 days from randomization. Additional imaging at Discontinuation Visit and Safety Follow-up Visit is not required provided that imaging assessments have been performed per schedule. Imaging will continue at the protocol defined interval until the time of PD, pregnancy, or the start of a new cancer treatment

14 Subjects who discontinue trial treatment for a reason other than disease progression will move into the Follow-up Phase and should be assessed every 9 weeks (63 ± 7 days) by radiologic imaging to monitor disease status. Follow-up Visit 1 should be scheduled 3 months after the last dose of trial treatment. Follow-up Visit 2 should occur 6 months after the last dose of trial treatment. After Follow-up Visit 2 subjects only need to be assessed every 9 weeks (63 ± 7 days) by radiologic imaging to monitor disease status, development of drug related SAEs and ECIs, and initiation of new antineoplastic therapy. Unless otherwise noted in the flow chart, every effort should be made to collect subject information until the start of new antineoplastic therapy, disease progression or death, whichever occurs first.

15 Vital signs to include temperature, pulse, respiratory rate, blood pressure, and weight.

16 Every effort should be made to collect blood samples at the Safety Follow Up Visit, Follow Up Visit 1, and Follow Up Visit 2 until the start of new antineoplastic therapy, disease progression or death, whichever comes first.

6.4 Cross Over Phase

(Only applicable for subjects randomized to SOC that have confirmation of PD by blinded independent central radiology review and qualified for the Crossover Phase).

	Treatment Cycles[1]														**End of Treatment Phase**		**Observation Phase[14] (pre-PD)**	**Follow up Phase[16]**			**Survival Follow up[19]**
Treatment Cycle / Scheduled Time	1[8]	2	3	4	5	6	7	8	9	10	11	12	13	14 through 35	Discontinuation Visit[12]	Safety Follow up Visit [13]	Observation Visit	Follow up Visit 1	Follow up Visit 2	Follow up Visit 3 and beyond	Survival Follow up Visit 1 and Beyond
Scheduling Window (Days):[2]		± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	At Study Drug Discontinuation +/- 3	30 Days from Last Dose +/- 3	± 3	3 Months from Last Dose +/- 7	6 Months from Last Dose +/- 7	Every 3 Months after Visit 2+/- 7	Approx. Every 2 Months +/- 14
Administrative Procedures																					
Prior and Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Subsequent antineoplastic therapy status															X	X	X	X	X	X	X
Survival Status[19]	< ---------- >																				X
Clinical Procedures / Assessments																					
Review Adverse Events [17]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Full Physical Examination	X														X						
Directed Physical Examination		X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X		
Vital Signs and Weight [7]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
ECOG Performance Status	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Laboratory Procedures / Assessments: analysis performed by local laboratory																					
CBC with Differential [11]	X [3]	X	X	X	X	X	X	X	X	X		X		X	X	X	X[15]				

	Treatment Cycles[1]														End of Treatment Phase		Observation Phase[14] (pre-PD)	Follow up Phase[16]			Survival Follow up[19]
Treatment Cycle / Scheduled Time	1[8]	2	3	4	5	6	7	8	9	10	11	12	13	14 through 35	Discontinuation Visit[12]	Safety Follow up Visit [13]	Observation Visit	Follow up Visit 1	Follow up Visit 2	Follow up Visit 3 and beyond	Survival Follow up Visit 1 and Beyond
Scheduling Window (Days):[2]		± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	At Study Drug Discontinuation +/- 3	30 Days from Last Dose +/- 3	± 3	3 Months from Last Dose +/- 7	6 Months from Last Dose +/- 7	Every 3 Months after Visit 2+/- 7	Approx. Every 2 Months +/- 14
PT/INR and aPTT	X[3]																				
Comprehensive Chemistry Panel [11]	X[3]	X	X	X	X	X	X	X	X	X		X		X	X	X	X[15]				
Urinalysis[4]	X[3]				X				X				X	X	X	X	X[15]				
T3, FT4 and TSH [5]	X[3]	X		X		X		X		X		X		X	X	X	X[15]				
Patient Reported Outcomes (PRO)																					
EuroQol EQ-5D[9]	X																				
EORTC QLQ-C30 [9]	X																				
EORTC QLQ-LC13 [9]	X																				
Oncology Health Economic Assessment [9]	X	X	X	X	X	X	X	X		X		X		X	X	X	X				
Efficacy Measurements																					
Tumor Imaging[6]			x			x			x			x		x	X	X	X	X[18]	X[18]	X[18]	
Study Drug Administration																					
Pembrolizumab[10]	X	X	X	X	X	X	X	X	X	X	X	X	X	X							

1 In general, assessments/procedures are to be performed on Day 1 and prior to the first dose of trial treatment for each cycle unless otherwise specified. Treatment cycles are 3 weeks (21-days). If treatment cycles are adjusted all procedures except imaging will be completed according to the Cycle number and not weeks on treatment, imaging will be performed every 9 weeks (± 7 days) from the first dose of trial treatment regardless of any treatment delays.
2 In general, the window for each visit is ± 3 days unless otherwise specified.
3 Laboratory tests for screening are to be performed within 10 days prior to the first dose of trial treatment. See Section 7.1.3 for details regarding laboratory tests.
4 After Cycle 1, lab samples can be collected up to 48 hours prior to the scheduled time point. Laboratory results must be known and acceptable prior to dosing. See Section 7.1.3 for details regarding laboratory tests; perform every 6 cycles after cycle 14.

	Treatment Cycles[1]														End of Treatment Phase		Observation Phase[14] (pre-PD)	Follow up Phase[16]			Survival Follow up[19]
Treatment Cycle / Scheduled Time	1[8]	2	3	4	5	6	7	8	9	10	11	12	13	14 through 35	Discontinuation Visit[12]	Safety Follow up Visit [13]	Observation Visit	Follow up Visit 1	Follow up Visit 2	Follow up Visit 3 and beyond	Survival Follow up Visit 1 and Beyond
Scheduling Window (Days):[2]		± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	At Study Drug Discontinuation +/- 3	30 Days from Last Dose +/- 3	± 3	3 Months from Last Dose +/- 7	6 Months from Last Dose +/- 7	Every 3 Months after Visit 2+/- 7	Approx. Every 2 Months +/- 14

5 After Cycle 1, lab samples can be collected up to 48 hours prior to the scheduled time point. Laboratory results must be known and acceptable prior to dosing. See Section 7.1.3 for details regarding laboratory tests; perform every 2 cycles after Cycle 13. Thyroid function tests will be performed by a central laboratory only if the local laboratory is unable to perform this service.

6 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 9 weeks (63 days±7 days) until the subject starts another anti-cancer treatment. Assessment of disease response or progression will be determined by the investigator. The treating physician will record a physician assessed tumor response and the criteria used i.e. modified RECIST 1.1 or standard RECIST v 1.1 on the discontinuation form. Imaging assessments should be performed every 9 weeks (+/- 7 days from crossover. Additional imaging at Discontinuation Visit and Safety Follow-up Visit is not required provided that imaging assessments have been performed per schedule. Imaging will continue at the protocol defined interval until the time of PD, pregnancy, or the start of a new cancer treatment.

7 Vital signs to include temperature, pulse, respiratory rate, weight and blood pressure.

8 Screening can initiate once progressive disease have been verified by the blinded independent central radiology review. Treatment with Pembrolizumab should not initiate until at least 30 days from the date of last dose of chemotherapy. 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.

9 PROs are to be administered by trained site personnel and completed electronically by subjects at cross-over treatment cycle 1 prior to all other study procedures and receiving results of any tests. The PROs should be administered in the following order: EuroQol EQ-5D followed by EORTC QLQ-C30 and then EORTC QLQ-LC13. The Oncology HEA will be completed every cycle between cycles 1 to 8 and then every other cycle thereafter. The Oncology HEA will also be obtained at the Treatment Discontinuation Visit and 30-day Safety Follow-up Visit. If the Treatment Discontinuation Visit occurs 30 days from the last dose of study treatment, at the time of the mandatory Safety Follow up Visit, the HEA does not need to be repeated. During the Observation phase, the HEA should continue to be assessed every 6 weeks until PD. The Oncology HEA will be administered and completed by qualified site personnel after the subject completes all other questionnaires and prior to all other study procedures.

10 Treatment with Pembrolizumab should not initiate until at least 30 days from the date of verified disease progression. Pembrolizumab can be administered for up to 35 cycles.

11 After Cycle 1, lab samples can be collected up to 48 hours prior to the scheduled time point. Laboratory results must be known and acceptable prior to dosing. See Section 7.1.3 for details regarding laboratory tests. CBC and chemistry will be performed every cycle up to cycle 10, then every other cycle.

12 The Discontinuation Visit should occur at the time study drug is discontinued for any reason. If the Discontinuation Visit occurs 30 days from the last dose of study treatment, at the time of the mandatory Safety Follow up Visit, procedures do not need to be repeated. Imaging assessments should be performed every 9 weeks (+/- 7 days from crossover. Additional imaging at Discontinuation Visit and Safety Follow-up Visit is not required provided that imaging assessments have been performed per schedule. Imaging will continue at the protocol defined interval until the time of PD, pregnancy, or the start of a new cancer treatment.

13 The mandatory Safety Follow-up Visit for all subjects should be conducted approximately 30 days after the last dose of trial treatment or before the initiation of new antineoplastic treatment, whichever comes first. Subjects with an AE of Grade >1 will be further followed until the resolution of the AE to Grade 0-1 or until beginning of a new antineoplastic therapy, whichever occurs first. Subjects who are eligible for treatment with pembrolizumab during the Second Course Phase may have up to three Safety Follow-up Visits, one after the Treatment Phase, Crossover Phase and the Second Course Phase. If the Discontinuation Visit occurs approximately 30 days (+/- 3 days) from last dose trial treatment the same procedures do not need to be repeated for the Safety Follow-up Visit. Imaging assessments should be performed every 9 weeks (+/- 7 days from crossover. Additional imaging at Discontinuation Visit and Safety Follow-up Visit is not required provided that imaging assessments have been performed per schedule. Imaging will continue at the protocol defined interval until the time of PD, pregnancy, or the start of a new cancer treatment

14 The Observation Phase is for any subject that discontinued study treatment for reasons other than pregnancy or PD (i.e., toxicity). Pembrolizumab subjects remain in the Observation Phase until the time of PD, pregnancy, or the start of a new antineoplastic therapy. Observation visits should begin 4 weeks (28 days +/- 7 days) from the Safety Follow-up Visit and follow a Q3W (21 days +/- 3

	Treatment Cycles[1]														End of Treatment Phase		Observation Phase[14] (pre-PD)	Follow up Phase[16]			Survival Follow up[19]
Treatment Cycle / Scheduled Time	1[8]	2	3	4	5	6	7	8	9	10	11	12	13	14 through 35	Discontinuation Visit[12]	Safety Follow up Visit [13]	Observation Visit	Follow up Visit 1	Follow up Visit 2	Follow up Visit 3 and beyond	Survival Follow up Visit 1 and Beyond
Scheduling Window (Days):[2]		± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	At Study Drug Discontinuation +/- 3	30 Days from Last Dose +/- 3	± 3	3 Months from Last Dose +/- 7	6 Months from Last Dose +/- 7	Every 3 Months after Visit 2+/- 7	Approx. Every 2 Months +/- 14

days) schedule thereafter. Tumor imaging for the Observation Visits should be maintained Q9W by following the same calendar day schedule that was initiated during Treatment Cycles. For subjects who have received at least 15 treatment cycles of pembrolizumab, the frequency of tumor imaging may be reduced to every 12 weeks (84 +/- 7 days) during the Observation Visits.

15 During the Observation Phase, these laboratory assessments should be obtained every 12 weeks.

16 Subjects who stop pembrolizumab after 35 trial treatments and have achieved PR and/or SD OR have achieved a CR (see section 7.1.5.5) will move to the Follow up Phase of the study. Follow up visit 1 should take place 3 months after the last dose of trial treatment. Follow up visit 2 should take place 6 months after last dose of trial treatment and additional Follow up visits should take place every 3 months thereafter. Subjects who experience disease progression (and do not continue into the Second Course Phase) or start a new antineoplastic therapy will move directly into Survival Follow up. For subject convenience, all Follow up assessments may occur during the same visit as the imaging studies are obtained. Subjects with an AE of Grade >1 will be further followed until the resolution of the AE to Grade 0-1 or until beginning of a new antineoplastic therapy, whichever occurs first.

17 Once a subject discontinues study treatment, report all SAEs (related and unrelated to trial treatment), ECIs, and irAEs occurring within 90 days following cessation of treatment or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier. After this time, report only SAEs and ECIs that are considered related to trial treatment.

18 Tumor imaging is not needed for subjects who start another anti-cancer treatment regimen.

19 Once the subject stops the imaging assessments for this protocol (e.g. for PD or starting a new antineoplastic therapy), the subject moves into the Survival Follow-up Phase and should be contacted by telephone approximately every 2 months to assess for survival status. Post-study treatments and the subject's response to them will also be collected. Updated survival status may be requested by the Sponsor at any time during the course of the study. Upon Sponsor notification, all subjects who do not/will not have a scheduled study visit or study contact during the Sponsor-defined time period will be contacted for their survival status (excluding subjects who have a death event previously recorded).

6.5 Amendment 08, Pembrolizumab Arm: Treatment and Follow-up Phase

	Treatment Cycles[1]													**End of Treatment Phase**		**Follow up Phase[11]**			**Survival Follow up[13]**
Treatment Cycle / Scheduled Time	1	2	3	4	5	6	7	8	9	10	11	12	13 and Beyond	Discontinuation Visit[9]	Safety Follow up Visit[10]	Follow up Visit 1	Follow up Visit 2	Follow up Visit 3 and Beyond	Survival Follow up Visit 1 and Beyond
Scheduling Window (Days):[2]	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	At Study Drug Discontinuation +/- 3	30 days from Last Dose +/- 3	3 Months from Last Dose +/- 7	6 Months from Last Dose +/- 7	Every 3 Months after Visit 2 +/- 7	Approx. Every 2 Months +/- 14
Administrative Procedures																			
Review Prior and Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Subsequent antineoplastic therapy status														X	X	X	X	X	X
Survival Status[13]	< ---------- >																		X
Clinical Procedures / Assessments																			
Review Adverse Events[12]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	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 [7]	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		
Study Drug Administration																			
Pembrolizumab[6]	X	X	X	X	X	X	X	X	X	X	X	X	X						

	Treatment Cycles[1]													End of Treatment Phase		Follow up Phase[11]			Survival Follow up[13]
Treatment Cycle / Scheduled Time	1	2	3	4	5	6	7	8	9	10	11	12	13 and Beyond	Discontinuation Visit[9]	Safety Follow up Visit[10]	Follow up Visit 1	Follow up Visit 2	Follow up Visit 3 and Beyond	Survival Follow up Visit 1 and Beyond
Scheduling Window (Days):[2]	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	At Study Drug Discontinuation +/- 3	30 days from Last Dose +/- 3	3 Months from Last Dose +/- 7	6 Months from Last Dose +/- 7	Every 3 Months after Visit 2 +/- 7	Approx. Every 2 Months +/- 14
Local Laboratory Procedures / Assessments																			
CBC with Differential[8]			X			X			X			X	X	X	X				
Comprehensive Chemistry Panel[8]			X			X			X			X	X	X	X				
Urinalysis[3]					X				X				X	X	X				
T3,FT4 and TSH[4]		X		X		X		X		X		X	X	X	X				
Efficacy Measurements																			
Tumor Imaging[5]			X			X			X			X	X	X	X	X[14]	X[14]	X[14]	

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

2 In general, the window for each visit is +/- 3 days unless otherwise specified.

3 After Cycle 1, lab samples can be collected up to 48 hours prior to the scheduled time point. Laboratory results must be known and acceptable prior to dosing. See Section 7.1.3 for details regarding laboratory tests. Perform every 4 cycles after Cycle 13.

4 Thyroid function tests will be performed by a central laboratory only if the local laboratory is unable to perform this service. After Cycle 1, lab samples can be collected up to 48 hours prior to the scheduled time point. Laboratory results must be known and acceptable prior to dosing. See Section 7.1.3 for details regarding laboratory tests. Performed every 2 cycles after Cycle 13.

5 On study imaging will be performed every 9 weeks (63 ± 7 days) calculated from the randomization date or more frequently if clinically indicated. The timing for imaging studies should follow calendar days and should not be adjusted for delays in cycle starts. The same imaging technique should be used in a subject throughout the trial. Imaging assessments should be performed every 9 weeks (+/- 7) days from randomization. Additional imaging at Discontinuation Visit and Safety Follow-up Visit is not required provided that imaging assessments have been performed per schedule. Imaging will continue at the protocol defined interval until the time of PD, pregnancy, or the start of a new cancer treatment.

6 Pembrolizumab can be administered for up to 35 treatments.

	Treatment Cycles[1]													End of Treatment Phase		Follow up Phase[11]			Survival Follow up[13]
Treatment Cycle / Scheduled Time	1	2	3	4	5	6	7	8	9	10	11	12	13 and Beyond	Discontinuation Visit[9]	Safety Follow up Visit[10]	Follow up Visit 1	Follow up Visit 2	Follow up Visit 3 and Beyond	Survival Follow up Visit 1 and Beyond
Scheduling Window (Days):[2]	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	At Study Drug Discontinuation +/- 3	30 days from Last Dose +/- 3	3 Months from Last Dose +/- 7	6 Months from Last Dose +/- 7	Every 3 Months after Visit 2 +/- 7	Approx. Every 2 Months +/- 14

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

8 After Cycle 1, lab samples can be collected up to 48 hours prior to the scheduled time point. Laboratory results must be known and acceptable prior to dosing. See Section 7.1.3 for details regarding laboratory tests. CBC and chemistry will be performed every3 cycles.

9 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.

10 The mandatory Safety Follow-up Visit for all subjects should be conducted approximately 30 days after the last dose of trial treatment or before the initiation of new antineoplastic treatment, whichever comes first. Subjects with an AE of Grade >1 will be further followed until the resolution of the AE to Grade 0-1 or until beginning of a new antineoplastic therapy, whichever occurs first. Subjects who are eligible for treatment with pembrolizumab during the Second Course Phase may have up to three Safety Follow-up Visits, one after the Treatment Phase, Crossover Phase and the Second Course Phase. If the Discontinuation Visit occurs approximately 30 days (+/- 3 days) from last dose trial treatment the same procedures do not need to be repeated for the Safety Follow-up Visit.

11 Subjects who stop pembrolizumab after 35 trial treatments and have achieved PR and/or SD OR have achieved CR (see section 7.1.5.5) will move to the Follow up Phase of the study. Follow up visit 1 should take place 3 months after the last dose of trial treatment. Follow up visit 2 should take place 6 months after last dose of trial treatment and additional Follow up visits should take place every 3 months thereafter. Subjects who experience disease progression (and do not continue into the Second Course Phase) or start a new antineoplastic therapy will move directly into Survival Follow up. For subject convenience, all Follow up assessments may occur during the same visit as the imaging studies are obtained. Subjects with an AE of Grade >1 will be further followed until the resolution of the AE to Grade 0-1 or until beginning of a new antineoplastic therapy, whichever occurs first.

12 Once a subject discontinues study treatment, report all SAEs (related and unrelated to trial treatment), ECIs, and irAEs occurring within 90 days following cessation of treatment or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier. After this time, report only SAEs and ECIs that are considered related to trial treatment.

13 During the Survival Follow-up Phase, the subject should be contacted by telephone approximately every 2 months to assess for survival status. Updated survival status may be requested by the Sponsor at any time during the course of the study. Upon Sponsor notification, all subjects who do not/will not have a scheduled study visit or study contact during the Sponsor-defined time period will be contacted for their survival status (excluding subjects who have a death event previously recorded).

14 Tumor imaging is not needed for subjects who start another anti-cancer treatment regimen.

6.6 Amendment 08, SOC Arm: Treatment and Follow-up Phase

	Treatment Cycles[1]													End of Treatment Phase		Survival Follow up[11]
Treatment Cycle / Scheduled Time	1	2	3	4	5	6	7	8	9	10	11	12	13 and Beyond	Discontinuation Visit[8]	Safety Follow up Visit[9]	Survival Follow up Visit 1 and beyond
Scheduling Window (Days):[2]	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	At Study Drug Discontinuation +/- 3	30 Days from Last Dose +/- 3	Approx. Every 2 Months +/- 14
Administrative Procedures																
Review Prior and Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Subsequent antineoplastic therapy status														X	X	X
Survival Status[11]	< ---------- >															X
Clinical Procedures / Assessments																
Review Adverse Events[10]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Directed Physical Examination	X	X	X	X	X	X	X	X	X	X	X	X	X		X	
Vital Signs and Weight [5]	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	
Study Drug Administration																
Carboplatin/Pemetrexed[4]	X	X	X	X	X	X	X	X	X	X	X	X	X			
Cisplatin/Pemetrexed[4]	X	X	X	X	X	X	X	X	X	X	X	X	X			
Paclitaxel/Carboplatin[4]	X	X	X	X	X	X	X	X	X	X	X	X	X			
Carboplatin/Gemcitabine	X	X	X	X	X	X										
Cisplatin/Gemcitabine	X	X	X	X	X	X										
Local Laboratory Procedures / Assessments																
CBC with Differential[6]			X			X			X			X	X	X	X	

	Treatment Cycles[1]													End of Treatment Phase		Survival Follow up[11]
Treatment Cycle / Scheduled Time	1	2	3	4	5	6	7	8	9	10	11	12	13 and Beyond	Discontinuation Visit[8]	Safety Follow up Visit[9]	Survival Follow up Visit 1 and beyond
Scheduling Window (Days):[2]	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	At Study Drug Discontinuation +/- 3	30 Days from Last Dose +/- 3	Approx. Every 2 Months +/- 14
Comprehensive Chemistry Panel[6]			X			X			X			X	X	X	X	
T3,FT4 and TSH[3]		X		X		X		X		X		X	X	X	X	
Efficacy Measurements																
Tumor Imaging[7]			X			X			X			X	X	X	X	

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

2 In general, the window for each visit is +/- 3 days unless otherwise specified.

3 Thyroid function tests will be performed by a central laboratory only if the local laboratory is unable to perform this service. After Cycle 1, lab samples can be collected up to 48 hours prior to the scheduled time point. Laboratory results must be known and acceptable prior to dosing. See Section 7.1.3 for details regarding laboratory tests. Performed every 2 cycles after Cycle 13.

4 This regimen to be administered up to a maximum of 6 cycles. Pemetrexed may be given after 4 cycles of Carboplatin/Pemetrexed, Cisplatin/Pemetrexed or Paclitaxel/Carboplatin in subjects with non-squamous histologies.

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

6 After Cycle 1, lab samples can be collected up to 48 hours prior to the scheduled time point. Laboratory results must be known and acceptable prior to dosing. See Section 7.1.3 for details regarding laboratory tests. CBC and chemistry will be performed every 3 cycles, and every 4 cycles after Cycle 13. Additional laboratory assessments required for the SOC platinum doublets offered in this trial, but not included in the above Flowchart, should be obtained per local guidance and results recorded in the appropriate CRF.

7 On study imaging will be performed every 9 weeks (63 ± 7 days) calculated from the randomization date or more frequently if clinically indicated. The timing for imaging studies should follow calendar days and should not be adjusted for delays in cycle starts. The same imaging technique should be used in a subject throughout the trial. Imaging assessments should be performed every 9 weeks (+/- 7) days from randomization. Additional imaging at Discontinuation Visit and Safety Follow-up Visit is not required provided that imaging assessments have been performed per schedule. Imaging will continue at the protocol defined interval until the time of PD, pregnancy, or the start of a new cancer treatment.

8 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.

9 The mandatory Safety Follow-up Visit for all subjects should be conducted approximately 30 days after the last dose of trial treatment or before the initiation of new antineoplastic treatment, whichever comes first. Subjects with an AE of Grade >1 will be further followed until the resolution of the AE to Grade 0-1 or until beginning of a new antineoplastic therapy, whichever occurs first. Subjects who are eligible for treatment with pembrolizumab during the Second Course Phase may have up to three Safety Follow-up Visits, one after the Treatment Phase, Crossover Phase and the Second Course Phase. If the Discontinuation Visit occurs approximately 30 days (+/- 3 days) from last dose trial treatment the same procedures do not need to be repeated for the Safety Follow-up Visit

10 Once a subject discontinues study treatment, report all SAEs (related and unrelated to trial treatment), ECIs, and irAEs occurring within 90 days following cessation of treatment or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier. After this time, report only SAEs and ECIs that are considered related to trial treatment.

11 During the Survival Follow-up Phase, the subject should be contacted by telephone approximately every 2 months to assess for survival status. Updated survival status may be requested by the Sponsor at any time during the course of the study. Upon Sponsor notification, all subjects who do not/will not have a scheduled study visit or study contact during the Sponsor-defined time period will be contacted for their survival status (excluding subjects who have a death event previously recorded).

6.7 Amendment 08, Second Course Treatment and Follow-up Phase

	Second Course Treatment Cycles[1]													End of Second Course Treatment		Survival Follow up[9]
Treatment Cycle / Scheduled Time	1	2	3	4	5	6	7	8	9	10	11	12	13	Discontinuation Visit	Safety Follow up Visit[12]	Survival Follow up Visit 1 and Beyond
Scheduling Window (Days):[2]		±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	At Study Drug Discontinuation +/- 3	30 Days from Last Dose +/- 3	Approx. Every 2 Months +/- 14
Administrative Procedures																
Eligibility Criteria	X															
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Subsequent antineoplastic therapy status															X	X
Survival status[9]	< ---------- >															X
Study Drug Administration																
Pembrolizumab[11]	X	X	X	X	X	X	X	X	X	X	X	X	X			
Clinical Procedures / Assessments																
Review Adverse Events[10]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Directed Physical Examination		X	X	X	X	X	X	X	X	X	X	X	X		X	
Vital Signs and Weight[13]	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	

	Second Course Treatment Cycles[1]													**End of Second Course Treatment**		**Survival Follow up**[9]
Treatment Cycle / Scheduled Time	1	2	3	4	5	6	7	8	9	10	11	12	13	Discontinuation Visit	Safety Follow up Visit[12]	Survival Follow up Visit 1 and Beyond
Scheduling Window (Days):[2]		±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	At Study Drug Discontinuation +/- 3	30 Days from Last Dose +/- 3	Approx. Every 2 Months +/- 14
Pregnancy Test -Urine or Serum β- HCG [3, 5]	X															
PT/INR and aPTT [4, 5]	X															
CBC with Differential [5, 8]	X		X			X			X			X		X	X[14]	
Comprehensive Chemistry Panel [5 8]	X		X			X			X			X		X	X[14]	
T3, FT4 and TSH[5,6]	X		X		X		X		X		X		X	X	X[14]	
Efficacy Measurements																
Tumor Imaging [7]	X			X			X			X			X	X	X	

1 In general, assessments/procedures are to be performed on Day 1 and prior to the first dose of trial treatment for each cycle unless otherwise specified. Treatment cycles are 3 weeks (21- days). If treatment cycles are adjusted all procedures except imaging will be completed according to the Cycle number and not weeks on therapy.

2 In general, the window for each visit is +/- 3 days unless otherwise specified.

3 For women of reproductive potential, a urine pregnancy test will be performed within 72 hours prior to the first Second Course dose. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test, performed by the local study site laboratory, will be required. Pregnancy tests (serum and/or urine tests) should be repeated if required by local guidelines.

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

5 Laboratory tests for determining eligibility for Second Course Phase are to be performed within 10 days prior to the first dose of pembrolizumab. See Section 7.1.3 for details regarding laboratory tests.

6 After the first dose, lab samples can be collected up to 48 hours prior to the scheduled time point. Laboratory results must be known and acceptable prior to dosing. See Section 7.1.3 for details regarding laboratory tests. Thyroid function tests will be performed by a central laboratory only if the local laboratory is unable to perform this service. Thyroid function tests should be performed every other cycle.

7 If the subject enters the Second Course Phase, Cycle 1 scan may be performed up to 30 days prior to the first dose of trial treatment in the Second Course Phase. Imaging will be performed every 9 weeks (63 +/-7 days) after the first dose of Second Course Phase trial treatment up until cycle 13 and every 12 weeks (84 +/- 7 days) thereafter. The timing of imaging should follow calendar days and should not be adjusted for delays in cycle starts. The same imaging technique should be used in a subject throughout the trial. Subjects who discontinue trial treatment due to reasons other than disease progression, should continue to be assessed every 9 weeks (63 +/- 7 days) by radiologic imaging until the start of a new antineoplastic therapy, documented disease progression, or death, whichever occurs first. If trial treatment is discontinued after cycle 13, tumor imaging should be performed every 12 weeks (84 days +/- 7 days). Continued imaging is not needed for subjects who start another antineoplastic treatment. The same imaging technique should be used in a subject throughout the trial. Imaging assessments should be performed every 9 weeks (+/- 7 days from randomization. Additional imaging at Discontinuation Visit and Safety Follow-up Visit is not required provided that imaging assessments have been performed per schedule. Imaging will continue at the protocol defined interval until the time of PD, pregnancy, or the start of a new cancer treatment

	Second Course Treatment Cycles[1]													End of Second Course Treatment		Survival Follow up[9]
Treatment Cycle / Scheduled Time	1	2	3	4	5	6	7	8	9	10	11	12	13	Discontinuation Visit	Safety Follow up Visit[12]	Survival Follow up Visit 1 and Beyond
Scheduling Window (Days):[2]		±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	At Study Drug Discontinuation +/- 3	30 Days from Last Dose +/- 3	Approx. Every 2 Months +/- 14

8 After the first dose, lab samples can be collected up to 48 hours prior to the scheduled time point. Laboratory results must be known and acceptable prior to dosing. See Section 7.1.3 for details regarding laboratory tests. CBC and chemistry will be performed every 3rd cycle.

9 Once a subject experiences disease progression or starts a new antineoplastic therapy, the subject moves into the Survival Follow-up Phase and should be contacted by telephone approximately every 2 months to assess for survival status and start of new antineoplastic therapy if applicable. During the Survival Follow-up Phase, the subject should be contacted by telephone approximately every 2 months to assess for survival status. Updated survival status may be requested by the Sponsor at any time during the course of the study. Upon Sponsor notification, all subjects who do not/will not have a scheduled study visit or study contact during the Sponsor-defined time period will be contacted for their survival status (excluding subjects who have a death event previously recorded).

10 Record all AEs occurring within 30 days after the last dose of trial treatment. Report all SAEs (related and unrelated to trial treatment), ECIs, and irAEs occurring within 90 days following cessation of treatment or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier. After this time, report only SAEs and ECIs that are considered related to trial treatment.

11 Pembrolizumab can be administered up to 17 trial treatment in Second Course Phase.

12 The mandatory Safety Follow-Up Visit should be conducted approximately 30 days after the last dose of trial treatment or before the initiation of a new antineoplastic treatment, whichever comes first. Subjects with an AE of Grade >1 will be further followed until the resolution of the AE to Grade 0-1 or until beginning of a new antineoplastic therapy, whichever occurs first. Subjects who are eligible per the requirements in Section 7.1.5.5 for treatment with pembrolizumab during the Second Course Phase may have up to three Safety Follow-up Visits, one after the Treatment Phase, Crossover Phase and the Second Course Phase.

13 Vital signs to include temperature, pulse, respiratory rate, blood pressure, and weight.

14 Every effort should be made to collect blood samples at the Safety Follow Up Visit until the start of new antineoplastic therapy, disease progression or death, whichever comes first.

6.8 Amendment 08, Cross Over Phase

(Only applicable for subjects randomized to SOC that have not started new anti-neoplastic therapy).

	Treatment Cycles[1]														**End of Treatment Phase**		**Follow up Phase[13]**			**Survival Follow up[15]**
Treatment Cycle / Scheduled Time	1[8]	2	3	4	5	6	7	8	9	10	11	12	13	14 through 35	Discontinuation Visit[11]	Safety Follow up Visit [12]	Follow up Visit 1	Follow up Visit 2	Follow up Visit 3 and Beyond	Survival Follow up Visit 1 and Beyond
Scheduling Window (Days):[2]		± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	At Study Drug Discontinuation +/-3	30 Days from Last Dose +/- 3	3 Months from Last Dose +/- 7	6 Months from Last Dose +/- 7	Every 3 Months after Visit 2 +/- 7	Approx. Every 2 Months +/- 14
Administrative Procedures																				
Prior and Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Subsequent antineoplastic therapy status															X	X	X	X	X	X
Survival Status[15]	< ---------- >																			X
Clinical Procedures / Assessments																				
Review Adverse Events [14]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	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 [7]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
ECOG Performance Status	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Laboratory Procedures / Assessments: analysis performed by local laboratory																				
CBC with Differential [10]	X [3]		X			X			X			X		X	X	X				
PT/INR and aPTT	X [3]																			
Comprehensive Chemistry Panel [10]	X [3]		X			X			X			X		X	X	X				

	Treatment Cycles[1]														End of Treatment Phase		Follow up Phase[13]			Survival Follow up[15]
Treatment Cycle / Scheduled Time	1[8]	2	3	4	5	6	7	8	9	10	11	12	13	14 through 35	Discontinuation Visit[11]	Safety Follow up Visit [12]	Follow up Visit 1	Follow up Visit 2	Follow up Visit 3 and Beyond	Survival Follow up Visit 1 and Beyond
Scheduling Window (Days):[2]		± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	At Study Drug Discontin-uation +/-3	30 Days from Last Dose +/- 3	3 Months from Last Dose +/- 7	6 Months from Last Dose +/- 7	Every 3 Months after Visit 2 +/- 7	Approx. Every 2 Months +/- 14
T3, FT4 and TSH [5]	X 3	X		X		X		X		X		X		X	X	X				
Efficacy Measurements																				
Tumor Imaging[6]			x			x			x			x		x	X	X	X[16]	X[16]	X[16]	
Study Drug Administration																				
Pembrolizumab[9]	X	X	X	X	X	X	X	X	X	X	X	X	X	X						

1 In general, assessments/procedures are to be performed on Day 1 and prior to the first dose of trial treatment for each cycle unless otherwise specified. Treatment cycles are 3 weeks (21-days). If treatment cycles are adjusted all procedures except imaging will be completed according to the Cycle number and not weeks on treatment.

2 In general, the window for each visit is ± 3 days unless otherwise specified.

3 Laboratory tests for screening are to be performed within 10 days prior to the first dose of trial treatment. See Section 7.1.3 for details regarding laboratory tests.

4 After Cycle 1, lab samples can be collected up to 48 hours prior to the scheduled time point. Laboratory results must be known and acceptable prior to dosing. See Section 7.1.3 for details regarding laboratory tests; perform every 6 cycles after cycle 14.

5 After Cycle 1, lab samples can be collected up to 48 hours prior to the scheduled time point. Laboratory results must be known and acceptable prior to dosing. See Section 7.1.3 for details regarding laboratory tests; perform every 2 cycles after Cycle 13. Thyroid function tests will be performed by a central laboratory only if the local laboratory is unable to perform this service.

6 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 9 weeks (63 days±7 days) until the subject starts another anti-cancer treatment. Assessment of disease response or progression will be determined by the investigator. The treating physician will record a physician assessed tumor response and the criteria used i.e. modified RECIST 1.1 or standard RECIST v 1.1 on the discontinuation form. Imaging assessments should be performed every 9 weeks (+/- 7 days from crossover. Additional imaging at Discontinuation Visit and Safety Follow-up Visit is not required provided that imaging assessments have been performed per schedule. Imaging will continue at the protocol defined interval until the time of PD, pregnancy, or the start of a new cancer treatment.

7 Vital signs to include temperature, pulse, respiratory rate, weight and blood pressure.

8 Treatment with Pembrolizumab should not initiate until at least 30 days from the date of last dose of chemotherapy. 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.

9 Pembrolizumab can be administered for up to 35 cycles.

10 After Cycle 1, lab samples can be collected up to 48 hours prior to the scheduled time point. Laboratory results must be known and acceptable prior to dosing. See Section 7.1.3 for details regarding laboratory tests. CBC and chemistry will be performed every 3rd cycle.

11 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.

12 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 Cycles[1]														**End of Treatment Phase**		**Follow up Phase[13]**			**Survival Follow up[15]**
Treatment Cycle / Scheduled Time	1[8]	2	3	4	5	6	7	8	9	10	11	12	13	14 through 35	Discontinuation Visit[11]	Safety Follow up Visit [12]	Follow up Visit 1	Follow up Visit 2	Follow up Visit 3 and Beyond	Survival Follow up Visit 1 and Beyond
Scheduling Window (Days):[2]		± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	At Study Drug Discontin-uation +/-3	30 Days from Last Dose +/- 3	3 Months from Last Dose +/- 7	6 Months from Last Dose +/- 7	Every 3 Months after Visit 2 +/- 7	Approx. Every 2 Months +/- 14

treatment, whichever comes first. Subjects with an AE of Grade >1 will be further followed until the resolution of the AE to Grade 0-1 or until beginning of a new antineoplastic therapy, whichever occurs first. Subjects who are eligible for treatment with pembrolizumab during the Second Course Phase may have up to three Safety Follow-up Visits, one after the Treatment Phase, Crossover Phase and the Second Course Phase. If the Discontinuation Visit occurs approximately 30 days (+/- 3 days) from last dose trial treatment the same procedures do not need to be repeated for the Safety Follow-up Visit.

13 Subjects who stop pembrolizumab after 35 trial treatments and have achieved PR and/or SD OR have achieved a CR (see section 7.1.5.5) will move to the Follow up Phase of the study. Follow up visit 1 should take place 3 months after the last dose of trial treatment. Follow up visit 2 should take place 6 months after last dose of trial treatment and additional Follow up visits should take place every 3 months thereafter. Subjects who experience disease progression (and do not continue into the Second Course Phase) or start a new antineoplastic therapy will move directly into Survival Follow up. For subject convenience, all Follow up assessments may occur during the same visit as the imaging studies are obtained. Subjects with an AE of Grade >1 will be further followed until the resolution of the AE to Grade 0-1 or until beginning of a new antineoplastic therapy, whichever occurs first.

14 Once a subject discontinues study treatment, report all SAEs (related and unrelated to trial treatment), ECIs, and irAEs occurring within 90 days following cessation of treatment or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier. After this time, report only SAEs and ECIs that are considered related to trial treatment.

15 Once a subject experiences disease progression or starts a new antineoplastic therapy, the subject moves into the Survival Follow-up Phase and should be contacted by telephone approximately every 2 months to assess for survival status and start of new antineoplastic therapy if applicable. During the Survival Follow-up Phase, the subject should be contacted by telephone approximately every 2 months to assess for survival status. Updated survival status may be requested by the Sponsor at any time during the course of the study. Upon Sponsor notification, all subjects who do not/will not have a scheduled study visit or study contact during the Sponsor-defined time period will be contacted for their survival status (excluding subjects who have a death event previously recorded).

16 Tumor imaging is not needed for subjects who start another anti-cancer treatment regimen.

7.0 TRIAL PROCEDURES

7.1 Trial Procedures

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

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

7.1.1 Administrative Procedures

7.1.1.1 Informed Consent

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

7.1.1.1.1 General Informed Consent

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

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

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

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

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

7.1.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

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

7.1.1.2 Inclusion/Exclusion Criteria

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

7.1.1.3 Subject Identification Card

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

7.1.1.4 Medical History

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

7.1.1.5 Prior and Concomitant Medications Review

7.1.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the subject within 30 days before starting the trial. In addition, record all treatments for a prior cancer other than NSCLC even if taken greater than 30 days prior to Visit 1. Prior treatments for NSCLC will be recorded separately and not listed as a prior medication.

7.1.1.5.2 Concomitant Medications

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

7.1.1.6 Non-small cell lung cancer Disease Details and Treatments

7.1.1.6.1 Disease Details

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

7.1.1.6.2 Prior Treatment

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

7.1.1.6.3 Subsequent Antineoplastic Therapy Status

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

7.1.1.7 Assignment of Screening Number

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

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

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

7.1.1.8 Assignment of Randomization Number

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

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

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

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

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

7.1.2 Clinical Procedures/Assessments

7.1.2.1 Adverse Event 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 12.6). Toxicities will be characterized in terms including seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

An immune related adverse event (irAE) may be defined as an 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. Following the guidance described in Section 7.2.3.2., certain irAEs should also be reported to the Sponsor as ECIs. (See the separate guidance document in the administrative binder regarding the identification, evaluation and management of irAEs and ECIs).

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

7.1.2.2 Physical Exam

7.1.2.2.1 Full Physical Exam

The investigator or qualified designee will perform a complete physical exam during the screening period. Clinically significant abnormal findings should be recorded as medical history. The time points for full physical exam are described in Section 6 - 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 Lead Electrocardiogram (ECG)

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

7.1.2.5 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status (see Section 12.5) 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.

7.1.2.6 Tumor Imaging

The process for image collection and transmission to the central vendor can be found in the Site Imaging Manual. Tumor imaging may be performed by computed tomography (CT) (preferred) or magnetic resonance imaging (MRI), but the same imaging technique should be used in a subject throughout the trial. CT scan is the more commonly used modality and is strongly encouraged for images of the thorax, abdomen and pelvis. An MRI with contrast is suggested if a pelvis CT scan is not considered SOC. See Section 7.1.2.7 Brain Imaging for brain scan details.

The initial tumor imaging will be performed within 30 days of randomization date. Scans performed as part of routine clinical management are acceptable for use as the screening scan if they are of diagnostic quality and performed within 30 days of randomization date**.** The subject must have at least one radiographically measurable lesion per RECIST 1.1 per local reading. On-study imaging will be performed every 9 weeks (63 ± 7 days) from the date of randomization or more frequently if clinically indicated. Tumor timing should follow calendar days and should not be adjusted for delays in cycle starts. It must be emphasized that subjects continue to receive all assessments as outlined in the Flowchart until RECIST 1.1 defined progression is documented by blinded independent central radiology, including instances of study therapy discontinuation due to toxicity.

If RECIST 1.1 defined progression is documented by blinded independent central radiology review, then the subject may be discontinued from trial treatment unless, in the opinion of the investigator, the subject is deriving clinical benefit from the therapy and the subject does not have any signs or symptoms of clinically instability. Clinical stability is defined as following:

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

2) No decline in ECOG PS.

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

Immune related response criteria assessed by the blinded independent radiology review will be provided to the investigator at the time of RECIST 1.1 defined progression in order to aid in decisions regarding treatment continuation. If treatment is continued beyond RECIST 1.1 defined tumor progression, subsequent imaging assessments should be based upon modified RECIST criteria. Modified RECIST 1.1 is an adapted form of RECIST 1.1 to account for the unique tumor response seen in this class of therapeutics.

In modified RECIST 1.1, if imaging shows PD, tumor assessment may be repeated ≥ 4 weeks later at the site in order to confirm PD with the option of continuing treatment for clinically stable subjects (see Table 5 below).

In determining whether or not the tumor burden has increased or decreased, investigators should consider all target lesions as well as non-target lesions. Subjects that are deemed clinically unstable are not required to have repeat imaging for confirmation. If radiologic progression is confirmed at the subsequent scan then the subject will be discontinued from trial treatment unless, if in the opinion of the investigator, the subject is deriving clinical benefit and upon consultation with the Sponsor. If radiologic progression is not confirmed, then the subject should resume/continue trial treatment and have their next scan according to the every 9 weeks (63 ± 7 days) schedule.

Table 5 Imaging and Treatment Determinations After First Radiological Evidence of PD

	Clinically Stable		Clinically Unstable	
	Imaging	Treatment	Imaging	Treatment
1st radiologic evidence of PD	Repeat imaging at ≥ 4 weeks to confirm PD	May continue study treatment at the investigator's discretion while awaiting confirmatory scan	Repeat imaging at ≥ 4 weeks to confirm PD if possible.	Discontinue treatment
Repeat scan confirms PD	No additional imaging required if investigator does not see benefit. If Investigator sees benefit, continue regularly scheduled imaging assessments every 9 weeks (63 ± 7 days) while on treatment.	May continue treatment if investigator considers subject deriving clinical benefit	No additional imaging required	N/A
Repeat scan shows SD, PR or CR	Continue regularly scheduled imaging assessments every 9 weeks (63 ± 7 days) while on treatment.[a]	Continue study treatment at the investigator's discretion.	Continue regularly scheduled imaging assessments every 9 weeks (63 ± 7 days) while on treatment.[a]	May restart study treatment if condition has improved and/or clinically stable per investigator's discretion.

There is no requirement for PD to be confirmed ≥4 weeks later for subjects in the control arm (e.g. those not receiving pembrolizumab).

[a] Tumor imaging will be assessed first at 9 weeks (63 ± 7 days). Subsequent tumor imaging will be performed every 9 weeks (63 ± 7 days) until end of treatment for all subjects.

SD does not need to be confirmed ≥4 weeks later. Schedule of 9 weeks (63 ± 7 days) should be followed as per protocol.

Imaging during the Observation Phase should be obtained every 9 weeks (63 ± 7 days) until the subject experiences disease progression that has been confirmed by blinded independent central radiology review or starts a new antineoplastic therapy.

Subjects who move into the Second Course Phase will continue to have scans performed every 9 weeks (63 ± 7 days) after the first dose of Second Course Phase trial treatment for Year 1 and every 3 months thereafter.

The same imaging technique should be used in a subject throughout the trial. The processes for image collection, processing and transmission to the central vendor are in the Site Imaging Manual.

For Amendment 08, tumor imaging will no longer be required for RECIST v1.1 assessments in accordance with the end points of this trial. Imaging should still be conducted every 9 weeks to assess for tumor response, but will no longer be required to be submitted to the blinded independent central radiology review.

7.1.2.7 Brain Imaging

For patients with no previous history of brain metastases, screening brain imaging will need to be obtained. MRI is the preferred imaging modality however CT is acceptable if an MRI is clinically contraindicated. If lesions are identified, the lesions must be treated, regardless of symptoms. Two additional scans, obtained at least 4 weeks apart, should be obtained to document disease stability AFTER local treatment administration to the brain metastases has been completed. Subjects with previously treated brain metastases may participate provided they are stable, which is defined as lack of progression on two sets of imaging obtained at least four weeks prior. Stability as defined above should be documented prior to the first dose of trial treatment. In addition, any neurologic symptoms must have returned to baseline or resolved and the subject is not using steroids for at least three days prior to trial treatment. The screening brain scan may be collected up to 42 days prior to randomization.

7.1.2.8 Patient Reported Outcomes (PROs)

The EuroQol EQ-5D, EORTC QLQ-C30 and EORTC QLQ-LC13 questionnaires will be administered by trained site personal and completed electronically by the subjects prior to all other study procedures and receiving results of any tests. Every effort should be made to withhold any information regarding disease progression from the subject until AFTER the ePRO assessments have been obtained. The PROs are completed in the following order: EuroQol EQ-5D first, then EORTC QLQ-C30, and lastly the EORTC QLQ-LC13 at the time points specified in the Trial Flow Charts. The ePRO must be completed by the subject, themselves.

The Oncology Health Economic Assessment (HEA) form captures non-study related healthcare visits, including healthcare provider visits, emergency room (ER) visits, and hospitalizations (including admission and discharge dates and primary discharge diagnosis). It will be administered and completed by qualified site personnel after the subject completes

all other questionnaires and before other study procedures. HEA collection time points are specified in the Trial Flow Charts.

It is most relevant and strongly recommended that ePROs and HEAs are administered prior to drug administration, AE evaluation and disease status notification.

Following Amendment 08, PRO and HEA assessments will no longer be required.

7.1.2.9 Tumor Tissue Collection

Tumor tissue for biomarker analysis from formalin fixed paraffin embedded tumor tissue sample or newly obtained formalin fixed biopsy of a tumor lesion not previously irradiated must be provided in the form of a tissue block or unstained slides and received by the central vendor before randomization. If new scientific data emerge that indicate that an existing biopsy or surgical specimen is suboptimal for identification of subjects, then only new biopsies will be acceptable for determination of PD-L1 status. Only subjects whose tumors demonstrate strong PD-L1 expression are eligible for enrollment. A fine needle aspirate, EBUS or cytologic specimen will not be acceptable. Needle or excisional biopsies, or resected tissue is required. Newly obtained formalin fixed specimens are encouraged.

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

Detailed instructions for tissue collection, processing and shipment are provided in the operations/laboratory Manual. Older biopsy material or surgical specimens may be used to assess EGFR mutation status and ALK translocation status, if not already documented when the subject signs informed consent.

7.1.3 Laboratory Procedures/Assessments

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

7.1.3.1 Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

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

Table 6 Laboratory Tests

Hematology	**Chemistry**	**Urinalysis**	**Other**
Hematocrit	Albumin	Blood	Follicle Stimulating Hormone (FSH)
Hemoglobin	Alkaline phosphatase	Glucose	Serum β-human chorionic gonadotropin (β-hCG)
Platelet count	Alanine aminotransferase (ALT)	Protein	Total Triiodothyronine(T3) It is acceptable to use FT3 in place of T3 if that is considered standard of care at your site.
WBC (total and differential)	Aspartate aminotransferase (AST)	Specific gravity	Free thyroxine (FT4)
	Carbon Dioxide (CO2 or Bicarbonate If these tests are not done as part of standard of care in your region then these tests do not need to be performed.)	Microscopic exam, if abnormal results are noted	Thyroid stimulating hormone (TSH)
	Calcium		PT (INR)
	Chloride		aPTT
	Creatinine		PK
	Glucose		Blood for FBR
	Magnesium		Anti-pembrolizumab Antibodies
	Phosphorus		Blood for Genetics
	Potassium		
	Sodium		
	Total Bilirubin		
	Direct Bilirubin, if total bilirubin is elevated above the upper limit of normal		
	Total protein		
	Blood Urea Nitrogen (BUN): BUN or Urea should be collected per institutional standard. It is not required to perform both of these laboratory tests Urea: BUN or Urea should be collected per institutional standard. It is not required to perform both of these laboratory tests		
	Uric Acid		

Laboratory tests for screening or entry into the Second Course Phase should be performed within 10 days prior to the first dose of trial treatment. After Cycle 1, pre-dose laboratory procedures can be conducted up to 48 hours prior to dosing.

Results must be reviewed by the investigator or qualified designee and found to be acceptable prior to each dose of trial treatment.

All screening tests (both local and central) must be known and acceptable prior to randomization. All labs performed locally must be known and acceptable prior to dosing in Cycle 1 and beyond. Any non-screening test performed for Cycle 1 and beyond by central lab should be evaluated by the treating investigator when results are available.

Additional laboratory assessments required for the SOC platinum doublets offered in this trial, but not included in the Flowcharts, should be obtained per local guidance and results recorded in the appropriate CRF.

7.1.3.2 Pharmacokinetic Evaluations

7.1.3.2.1 Blood Collection for Serum Pembrolizumab

Sample collection, storage and shipment instructions for serum samples will be provided in the Procedures manual.

The time points for PK blood sampling are described in Section 6 - Trial Flow Chart. Blood samples for PK will be collected and stored only at this time. Further analysis may be performed if required.

Following Amendment 08, blood samples for PK measurements are no longer required.

7.1.3.3 Anti-Pembrolizumab Antibodies

Sample collection, storage and shipment instructions will be provided in the Procedures manual.

The time points for anti-pembrolizumab antibody blood sampling are described in Section 6 - Trial Flow Chart. Blood samples for anti-pembrolizumab antibodies will be collected and stored only at this time. Further analysis may be performed if required.

Following Amendment 08, blood samples for anti-pembrolizumab antibodies is no longer required.

7.1.3.4 Molecular Testing

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

7.1.3.5 Future Biomedical Research

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

- Blood for genomics use
- Leftover tumor tissue

7.1.4 Other Procedures

7.1.4.1 Withdrawal/Discontinuation

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

7.1.4.1.1 Withdrawal From Future Biomedical Research

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

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

7.1.4.2 Blinding/Unblinding

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

7.1.4.3 Calibration of Critical Equipment

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

Critical Equipment for this trial includes:

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

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

7.1.5 Visit Requirements

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

7.1.5.1 Screening

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

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

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

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

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

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

7.1.5.2 Treatment Phase

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

Subject should continue to receive all assessments as defined in the Treatment phase of the Flowchart while they are actively receiving treatment, which includes both SOC and pembrolizumab. This includes those subjects who are treated beyond RECIST v1.1 PD. Please note there is no difference in the frequency of assessments for those subjects who are treated beyond RECIST v1.1 defined PD.

7.1.5.3 End of Treatment Visits

7.1.5.3.1 Discontinuation Visit

The Discontinuation Visit should occur at the time study drug is discontinued for any reason. If the Discontinuation Visit occurs 30 days from the last dose of study treatment, at the time of the mandatory Safety Follow up Visit, procedures do not need to be repeated. Procedures at the time of discontinuation are detailed in Section **7**.1.5.3.2 Mandatory Safety Follow up Visit

7.1.5.3.2 Mandatory Safety Follow up Visit

The mandatory Safety Follow-Up Visit should be conducted approximately 30 days after the last dose of trial treatment or before the initiation of a new antineoplastic treatment, whichever comes first. Subjects with an AE of Grade >1 will be further followed until the resolution of the AE to Grade 0-1 or until beginning of a new antineoplastic therapy, whichever occurs first. Subjects who are eligible per the requirements in Section 7.1.5.5 for treatment with pembrolizumab during the Second Course Phase may have up to two Safety Follow-up Visits, one after the Treatment Phase and the second after the Second Course Phase.

7.1.5.3.3 Observation Visit

Subjects who complete their fixed number of 4 - 6 cycles of SOC or who stop either SOC (including pemetrexed maintenance) or pembrolizumab for reasons other than PD or pregnancy, should move into the Observation Phase of the study and complete the assessments in the Observation Visits schedule as outlined in the study flow chart in Section 6.

Subjects randomized to pembrolizumab who discontinue therapy due to a PR and/or SD after 35 trial treatments should follow procedures in the End of Treatment Phase and Follow-up Phase of the study. If PD is established by the site during the assessments obtained during the Follow-up Phase of the study, the subject may be eligible for the Second Course Phase. Laboratory tests including CBC, thyroid function tests, comprehensive chemistry panel and urinalysis should be obtained every 3 months during the Observation Visit Phase.

Following Amendment 08, the Observation Visits will no longer be required. Subjects receiving SOC may proceed directly to Crossover if they meet the requirements outlined in section 7.1.5.6 below and will otherwise proceed directly to survival follow-up upon discontinuing SOC therapy. Subjects receiving pembrolizumab who would have previously continued with Observation Visits will now move directly into Survival Follow-up.

7.1.5.4 Follow up Phase

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

7.1.5.4.1 Follow-up Visits

Subjects who are randomized to pembrolizumab, or are receiving pembrolizumab on the Crossover Phase, and have received the maximum administrations of pembrolizumab OR who have achieved a CR (see criteria outlined in Section 7.1.5.5), should be followed as indicated in the Follow up Phase of the study outlined in Section 6.0. Follow-up Visit 1 should be scheduled 3 months after the last dose of trial treatment. Assessment for drug-related immune-related AEs should occur at Follow-up Visit 1. Follow-up Visit 2 should occur 6 months after the last dose of trial treatment. Unless otherwise noted in the flowchart, every effort should be made to collect subject information on the start of new antineoplastic therapy, disease progression and death.

Subjects who are eligible to receive re-treatment with pembrolizumab according to the criteria in Section 7.1.5.5 will move to the Second Course Phase when they experience disease progression. Imaging should be performed every 9 weeks to assess tumor response.

7.1.5.4.2 Survival Follow-up

Once the subject stops the imaging assessments for this protocol (e.g. for PD or starting a new antineoplastic therapy), the subject moves into the survival follow-up phase and should be contacted by telephone approximately every 2 months to assess for survival status. Post-study treatments and the subject's response to them will also be collected.

7.1.5.5 Second Course Phase

Visit requirements are outlined in Section 6.0 - Trial Flow Chart. Specific procedure-related details are provided above in Section 7.1 - Trial Procedures. Subjects who were randomized to receive pembrolizumab may be eligible to receive pembrolizumab for 17 cycles in the Second Course Phase of this study if the subject:

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

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

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

OR

- Had SD, PR or CR and stopped pembrolizumab treatment after 24 months of study therapy for reasons other than disease progression or intolerability.

- Experienced PD during treatment, yet continued to receive pembrolizumab beyond progression and attained subsequent benefit, completing 24 months without further disease progression or intolerability.

AND

- Continues to meet inclusion criteria 4, 5, 6, 11, 12, and 13.

- Continues to meet exclusion criteria 4, 5, 8 to 17 and/or 18.

Subjects will be re-treated at the same dose as when they last received pembrolizumab. An objective response or progression of disease assessed by investigator reviewed RECIST 1.1 that occurs during the Second Course Phase for a subject will not be counted as an event for the primary analysis of either endpoint in this trial.

7.1.5.6 Crossover for Subjects in the Chemotherapy Arm

Subjects on the SOC arm with documented disease progression following chemotherapy, are eligible to participate in the crossover arm of this trial. 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. Crossover subjects may not initiate treatment with pembrolizumab any earlier than 30 days after their last dose of chemotherapy regardless of the time of progression. Of note, the 30 day safety follow up visit may occur on the same day as the first dose of pembrolizumab in the Crossover Phase. Subjects who are being observed for progression in the Observation Phase should not initiate therapy with pembrolizumab until PD has been verified by blinded independent central review.

Crossover Qualifications:

Subjects on the SOC arm will be considered for crossover to pembrolizumab after documented, progressive disease per RECIST 1.1 guidelines (based on centrally reviewed assessment). Crossover is optional and is at the discretion of the Investigator (with the SPONSORs agreement). Imaging must be completed to establish a new baseline for the Crossover Phase.

Subjects who meet the following criteria are eligible for crossover:

- Chemotherapy induced AEs (except alopecia) must have improved to CTCAE (Version 4.0) ≤Grade 1
- Have adequate organ function as indicated by the laboratory values in Table 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
- Documentation of progressive disease per RECIST v1.1 by a blinded independent central review
- Subject has not received any other systemic anticancer therapies other than the SOC platinum doublet administered during the treatment phase.
- Subject has not received palliative radiotherapy of 30Gy or less within 7 days of the first dose of trial treatment.

Subjects who crossover and then achieve a CR per RECIST 1.1 have the option to hold pembrolizumab. Additional details are provided in Second Course Phase Section 7.1.5.5. Subjects who permanently discontinue the Crossover Phase will follow the same Survival Follow-up assessments outlined in Section 6.

Following Amendment 08, documented progressive disease per RECIST 1.1 is no longer a requirement for Crossover. Subjects randomized to SOC and who have not received an anti-PD-1 therapy may crossover to pembrolizumab. All other criteria remain in effect to ensure subject safety.

7.1.5.7 Survival Status

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

7.2 Assessing and Recording Adverse Events

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

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

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

Adverse events may occur during the course of the use of the Sponsor's product in clinical trials or within the follow-up period specified by the protocol, or prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

Adverse events may also occur in screened subjects during any pre-allocation baseline period as a result of a protocol-specified intervention, including washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

Progression of the cancer under study is not considered an adverse event unless it is considered to be drug related by the investigator.

All adverse events will be recorded from the time the consent form is signed through 30 days following cessation of treatment and 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.

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 any of the treatments: five times the pembrolizumab dose or more than 20% of the chemotherapy regimen. No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, pembrolizumab or the chemotherapy regimen 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 within 24 hours to the Sponsor either by electronic media or paper. Sponsor Contact information can be found in the Investigator Trial File Binder (or equivalent).

7.2.2 Reporting of Pregnancy and Lactation to the Sponsor

Although pregnancy and lactation are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them) that occurs during the trial or within 120 days of completing the trial or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier. All subjects who become pregnant must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

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

7.2.3 Immediate Reporting of Adverse Events to the Sponsor

7.2.3.1 Serious Adverse Events

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

- Results in death;
- Is life threatening;
- Results in persistent or significant disability/incapacity;
- Results in or prolongs an existing inpatient hospitalization;
- Is a congenital anomaly/birth defect;
- Is a new cancer (that is not a condition of the study);
- Is associated with an overdose;
- Is an other important medical event

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

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 information) that occurs to any subject from the time the consent is signed through 90 days following cessation of treatment or 30 days following cessation of treatment if the subject initiate new anticancer therapy, whichever is earlier, whether or not related to the Sponsor's product, must be reported within 24 hours to the Sponsor either by electronic media or paper. Sponsor Contact information can be found in the Investigator Trial File Binder (or equivalent).

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

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

7.2.3.2 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be recorded as such on the Adverse Event case report forms/worksheets and reported within 24 hours to the Sponsor either by electronic media or paper. Sponsor Contact information can be found in the Investigator Trial File Binder (or equivalent).

Events of clinical interest for this trial include:

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

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

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

3. Additional adverse events:

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

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

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

7.2.3.3 Protocol-Specific Exceptions to Serious Adverse Event Reporting

Efficacy endpoints as outlined in this section will not be reported to the Sponsor as described in Section 7.2.3. - Immediate Reporting of Adverse Events to the Sponsor, unless there is evidence suggesting a causal relationship between the drug and the event. Any such event will be submitted to the Sponsor within 24 hours either by electronic or paper media.

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

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

7.2.4 Evaluating Adverse Events

An investigator who is a qualified physician will evaluate all adverse events according to the NCI Common Terminology for Adverse Events (CTCAE), version 4. Any adverse event which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the adverse event case report forms/worksheets.

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

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

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

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

7.2.5 Sponsor Responsibility for Reporting Adverse Events

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

7.3 TRIAL GOVERNANCE AND OVERSIGHT

7.3.1 Scientific Advisory Committee

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

7.3.2 Executive Oversight Committee

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

7.3.3 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 include 3 clinicians experienced in Lung Cancer and 1 external statistician; this is in addition to the unblinded trial statistician who will be a non-voting member of the committee.

The DMC will make recommendations to the EOC regarding steps to ensure both subject safety and the continued ethical integrity of the trial. Also, the DMC will review interim trial results, consider the overall risk and benefit to trial participants (see Section 8.1.5 - Interim Analyses) and recommend to the EOC if the trial should continue in accordance with the protocol.

Specific details regarding 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 DMC Charter.

7.3.3.1 Post Final Analysis Activities

If the DMC recommends crossover of patients from standard of care to pembrolizumab based upon positive OS observed at either the interim PFS analysis or final OS analysis, all patients with a randomization number in this study, if they still meet certain inclusion criteria, may be offered further therapy with pembrolizumab; the details of which will be discussed in a future communication.

8.0 STATISTICAL ANALYSIS PLAN

8.1 Statistical Analysis Plan Summary

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

8.1.1 Efficacy Analyses

The intention-to-treat (ITT) population that includes all randomized subjects will serve as the primary population for the analyses of efficacy data in this trial. The primary efficacy endpoint is PFS (i.e., time from randomization to documented progressive disease or death due to any cause, whichever occurs first) per RECIST 1.1 based on blinded independent radiologists' review. The secondary efficacy endpoints for this trial are OS and ORR per RECIST 1.1 based on blinded independent radiologists' review. An outline of the analysis strategy for key efficacy endpoints is presented in Table 8 below. The analysis plan for PROs will be provided in a separate document before the final PFS analysis.

Table 8 Analysis Strategy for Key Efficacy Endpoints

Endpoint (Description, Time Point)	Statistical Method	Analysis Population	Missing Data Approach
Primary			
PFS (RECIST 1.1 by blinded independent central radiology review)	Testing: Stratified Log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT	Model based
Secondary			
OS	Testing: Stratified Log-rank test Estimation: Stratified Cox model with Efron's tie handling method for estimation	ITT	Model based
ORR (RECIST 1.1 by blinded independent central radiology review)	Stratified Miettinen & Nurminen method	ITT	Subjects with missing data are considered non-responders

8.1.2 Safety Analyses

The All Subjects as Treated (ASaT) population will be used for the primary analysis of safety data in this study. Investigators will be asked to report adverse experiences at every visit on this study (at least every three weeks during treatment) using Common Terminology Criteria for Adverse Events, Version 4.0. The attribution to drug, time-of-onset, duration of the event, its resolution, and any concomitant medications administered will be reported. AEs will be analyzed and reported for between arm differences in various parameters, including but not limited to Events of Clinical Interest outlined in the separate ECI and irAE guidance document, all AEs, SAEs, fatal AEs, and laboratory changes. Safety analyses will follow a tiered approach.

In the primary safety comparison between pembrolizumab and control, subjects who cross over to pembrolizumab are censored at time of crossover (i.e., AEs occurring during treatment with pembrolizumab are excluded for control-arm subjects). An exploratory safety analysis will be conducted for the crossover population including all safety events starting from the date of first dose of pembrolizumab.

8.1.3 Multiplicity

The overall type I error rate for this study is strictly controlled at 2.5% (one-sided). There are one planned analysis of ORR, one planned analysis of PFS and two planned analyses of OS. The ORR analysis will occur when the first 191 randomized subjects have a minimum of 6 months of follow up, and will be tested at the 0.5% (one-sided) alpha level. PFS will be tested only once at the planned PFS analysis after ~175 PFS events are observed, and will be tested at the 2.5% (one-sided) level if ORR is positive or at the 2.0% (one-sided) level if ORR is negative. OS will be tested only if PFS is positive and at the same level as PFS (i.e., step-down).

For OS, a Hwang-Shih-DeCani alpha-spending function with the gamma parameter -0.4 and beta-spending function with gamma -35 are constructed to implement group sequential boundaries that control the type I error rate as well as allow for non-binding futility analysis.

If at least 110 OS events are observed at the planned PFS analysis after ~175 PFS events are observed, an interim OS analysis will be conducted at the level determined by the spending function and the actual number of OS events at the PFS analysis. The final OS analysis will occur when ~170 OS events are observed at the level determined by the spending function and the actual number of OS events observed at the PFS analysis.

However, if there are less than 110 OS events at the planned PFS analysis, a nominal alpha of 0.01% (negligible impact on overall type I error rate) will be spent on the OS hypothesis at the time of the planned PFS analysis to prevent the study from premature stopping. The next interim and final OS analyses will be conducted after ~110 and ~170 OS events are observed, respectively, at the alpha level determined by the spending function boundaries and actual number of OS events.

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

Following Amendment 08, the final OS analysis is no longer required and will not be performed as described above. This is due to the study hypothesis for OS being supported at the interim analysis with database cutoff of May 9, 2016.

8.1.4 Power and Sample Size

The study is event-driven and plans to randomize approximately 300 subjects with 1:1 ratio into the pembrolizumab arm and the SOC arm.

The planned ORR analysis will be conducted after the first 191 subjects have a minimum of 6 months of follow up. This analysis has ~95% power to detect a 30% difference in ORR (e.g., 32% in SOC versus 62% in pembrolizumab) at alpha=0.5%. An observed ORR difference of approximately 19% is needed to achieve a positive ORR outcome (e.g., 32% in SOC versus 51% in pembrolizumab).

The planned PFS analysis will be conducted after approximately 175 PFS events are observed between the pembrolizumab arm and control. If there are less than 110 OS events at the time, then the analysis may be delayed for up to two months or when the target OS number is reached, whichever occurs first. With ~175 PFS events, the study has ~98%/97% power to detect a HR of 0.55 at alpha = 2.5%/2% (one-sided) at the final PFS analysis. A *p*-value less than 2.5%/2% (one-sided) for PFS approximately corresponds to an empirical HR of <0.744/0.738 (or approximately at least 7.4/7.5 months of median PFS in pembrolizumab vs. 5.5 months of median PFS in SOC).

With ~110 OS events at interim OS analysis, the study has ~90% power to observe a HR <1 when the true HR is 0.7, assuming that half of the subjects in the control arm cross over to pembrolizumab at the time of analysis. The final OS analysis will be conducted after approximately 170 deaths have occurred between the pembrolizumab arm and control. With 170 OS events at final OS analysis, the study has ~75% power to observe a HR <1 assuming that ~70% of the subjects in the control arm cross over to pembrolizumab. With two planned OS analyses, i.e., ~110 OS events at final PFS analysis and ~170 OS events at the final OS analysis, the study has approximately 60%/57% power to detect a HR of 0.7 at the level of 2.5%/2.0% (one-sided). However, due to the anticipated high crossover rate, the actual power could be substantially lower. A 95% CI will be provided for HR to characterize the OS effect in case superiority is not demonstrated and the rank-preserving structural failure time model will be used for crossover adjustment. More details are provided in Section 8.2.7.

8.1.5 ORR, PFS and OS Analyses

There is one planned analysis of ORR, one planned analysis of PFS and two planned analyses of OS. Table 9 provides the summary of the interim analysis strategy assuming that ~110 OS events are observed at the time of the final PFS analysis.

Table 9 Summary of PFS and OS Analysis Strategies

ORR, PFS and OS Analyses	Key Endpoints	Expected Timing of Analysis	Sample size expected at time of analysis	Primary Purpose of Analysis
ORR analysis	• ORR	~16 months from study start	• First 191 subjects have at least 6 months follow up	• Demonstrate superiority of pembrolizumab in ORR
Final PFS analysis Interim OS analysis	• PFS (primary) • OS	~20 months from study start	• ~ 175 PFS (~110 OS) events between the pembrolizumab arm and the chemotherapy arm	• Demonstrate superiority of pembrolizumab in PFS • Examine OS effect of pembrolizumab
Final OS analysis	• OS	~28 months from study start	• ~170 OS events between the pembrolizumab arm and the chemotherapy arm	• Examine OS effect of pembrolizumab

Following Amendment 08, the final OS analysis is no longer required and will not be performed as described above. This is due to the study hypothesis for OS being supported at the interim analysis with database cutoff of May 9, 2016.

8.2 Statistical Analysis Plan

8.2.1 Responsibility for Analyses/In-House Blinding

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

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

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

Treatment-level results of the planned ORR and PFS analyses will be provided by an external unblinded statistician to the eDMC. Limited additional SPONSOR personnel may be unblinded to the treatment level results of the interim analyses, if required, in order to act on the recommendations of the eDMC or facilitate regulatory filing after the ORR/ PFS analysis. The extent to which individuals are unblinded with respect to results of interim analyses will be documented by the unblinded statistician.

The eDMC will serve as the primary reviewer of the results of the planned ORR and PFS analyses and the interim OS analysis, and will make recommendations for discontinuation of

the study or modification to an executive committee of the SPONSOR. If the eDMC recommends modifications to the design of the protocol or discontinuation of the study, this executive committee may be unblinded to results at the treatment level in order to act on these recommendations. Additional logistical details and data monitoring guidance will be provided in the eDMC Charter.

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

8.2.2 Hypotheses/Estimation

Objectives and hypotheses of the study are stated in Section 3. The study is considered to have met its primary objective if pembrolizumab is superior to SOC in PFS.

8.2.3 Analysis Endpoints

8.2.3.1 Efficacy Endpoints

Primary

Progression-free survival - RECIST 1.1

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

Secondary

Overall Survival

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

Objective response rate

Objective response rate is defined as the proportion of the subjects in the analysis population who have a complete response (CR) or partial response (PR). Responses are based upon blinded independent central radiologists' review per RECIST 1.1.

Exploratory

Exploratory endpoints of this study include PFS2, time to response, response duration, disease control rate as well as ORR, response duration, disease control rate, PFS and OS following crossover to pembrolizumab. Patient-reported outcomes (PROs) while on treatment and post-discontinuation will be examined.

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

Time to progression following crossover to pembrolizumab is defined as the time from the first dose of crossover therapy to the earliest documented disease progression (with respect to the last available tumor assessment prior to crossover). OS following crossover to pembrolizumab is defined as the time from the first dose of crossover therapy to death due to any cause.

8.2.3.2 Safety Endpoints

Safety measurements are described in Section 7.

8.2.4 Analysis Population

8.2.4.1 Efficacy Analysis Population

The analysis of primary efficacy endpoints are based on the intention -to-treat (ITT) population, i.e., subjects will be included in the treatment group to which they are randomized. Details on the approach to handling missing data are provided in Section 8.2.5 Statistical Methods.

8.2.4.2 Safety Analysis Populations

The All Subject as Treated (ASaT) population will be used for the analysis of safety data in this study. The ASaT population consists of all randomized subjects who received at least one dose of study treatment. Subjects will be included in the treatment group corresponding to the trial treatment they actually received for the analysis of safety data. Subjects who take incorrect trial treatment for the entire treatment period will be included in the treatment group corresponding to the trial treatment actually received. At least one laboratory or vital sign measurement obtained subsequent to at least one dose of trial treatment is required for inclusion in the analysis of each specific parameter. To assess change from baseline, a baseline measurement is also required.

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

8.2.5 Statistical Methods

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

8.2.5.1 Statistical Methods for Efficacy Analyses

The overall type I error rate for this study is strictly controlled at 2.5% (one -sided) that allows the trial to declare positive in ORR, PFS or OS (if PFS is significant) in the ITT population.

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

8.2.5.1.1 Progression-Free Survival

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. A stratified Cox proportional hazard model with Efron's method of tie handling will be used to assess the magnitude of the treatment difference (i.e., 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 same stratification factors used for randomization (see Section 5.4) will be applied to both the stratified log-rank test and the stratified Cox model.

Since disease progression is assessed periodically, progressive disease (PD) can occur any time in the time interval between the last assessment where PD was not documented and the assessment when PD is documented. 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, 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, two sensitivity analyses will be performed with a different set of censoring rules. Sensitivity analysis 1 is the same as the primary analysis except that it censors at the last disease assessment without PD when PD or death is documented after more than one missed disease assessment. Sensitivity analysis 2 is the same as the primary analysis except that it considers discontinuation of treatment or initiation of new anticancer treatment, whichever occurs later, to be a PD event for subjects without documented PD or death. The censoring rules for primary and sensitivity analyses are summarized in Table 10. In case there is an imbalance between the treatment groups on

disease assessment schedules or censoring patterns, we will also perform the following two additional PFS sensitivity analyses: 1) a PFS analysis using time to scheduled tumor assessment visit from randomization as opposed to actual tumor assessment time; 2) Finkelstein's likelihood-based score test for interval-censored data, which modifies the Cox proportional hazard model for interval censored data, will be used as a supportive analysis for the PFS endpoint. The interval will be constructed so that the left endpoint is the date of the last disease assessment without documented PD and the right endpoint is the date of documented PD or death, whichever occurs earlier.

Table 10 Censoring Rules for Primary and Sensitivity Analyses of PFS

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

8.2.5.1.2 Overall Survival

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

Since subjects in the control arm are expected to discontinue from the study earlier compared to subjects in the pembrolizumab arm because of earlier onset of PD and they may switch to the pembrolizumab treatment after the confirmed progressive disease, the Rank Preserving Structural Failure Time (RPSFT) model will be used to adjust for the effect of crossover on OS. The RPSFT model provides a randomization-based estimate of treatment effect (RBEE) corrected for the bias induced by crossover. The 95% CIs of the HR for OS after adjustment of the cross-over effect will be provided. The Kaplan-Meier estimates of the OS rate at time points of interest will also be compared between the two treatment groups to explore the

confounding effect of subsequent treatments. To further account for the possible confounding effect, a sensitivity analysis of OS that censors subjects at the time of initiation of new therapy will be performed and an OS analysis that treats initiation of new therapy as a time-dependent binary covariate will also be conducted. In case the proportional hazards assumption doesn't hold, Fleming and Harrington's weighted log-rank test or other methods, as appropriate, will be conducted, after proper adjustment of the crossover effect over time.

8.2.5.1.3 Objective response rate

Stratified Miettinen and Nurminen's method will be used for comparison of the ORRs between the treatment groups. A 95% CI for the difference in response rates between the pembrolizumab arm and the control as well as the *p*-value will be provided. The same stratification factors used for randomization (see Section 5.4) will be applied to the analysis. Sensitivity analyses will be performed for comparison of ORR based on investigator's assessment.

8.2.5.1.4 Exploratory analyses

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

The same approaches as previously described for primary analysis and secondary analysis will be applied to subjects who crossover to pembrolizumab after disease progression on the control arm (chemotherapy) in this study. The reference start time of PFS and OS is the time of first dose crossover therapy.

For subjects who cross over to pembrolizumab after disease progression on the control arm, time to progression while on the control arm will be compared to the time to progression following crossover, where the time to progression following crossover is defined as the time from time of crossover to the earliest documented disease progression. The last available tumor assessment before crossover will serve as the baseline for disease assessment post crossover. If the number of events permits, time to progression before and after crossover will be summarized descriptively using the Kaplan-Meier method.

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

EORTC QLQ-C30, EORTC QLQ-LC13, EuroQoL EQ-5D, Oncology Health Economic Assessment (HEA) and tumor volumetric changes will be summarized as part of the exploratory analysis. Longitudinal and descriptive data analysis will be used to evaluate

patient-reported outcomes (PRO). Several approaches will be considered to address the issue of informative missing data, for example, (i) truncating the analysis observation period at the visit closest to median duration of treatment in the comparator arm, and (ii) hierarchical pattern mixture models incorporating reason for missingness (a model that treats disease progression as a time-varying covariate). The difference in PRO score for progressed subjects compared to subjects with no radiographic evidence of tumor progression will be evaluated within each treatment arm. For HEA, descriptive statistics by treatment group will include total counts of each type of healthcare contact, as well as the total number of hospital days. The detailed PRO analysis plan will be included in a separate document.

8.2.5.2 Statistical Methods for Safety Analyses

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

The analysis of safety results will follow a tiered approach (Table 11). The tiers differ with respect to the analyses that will be performed. Safety parameters or adverse experiences of special interest that are identified *a priori* constitute "Tier 1" safety endpoints that will be subject to inferential testing for statistical significance with p-values and 95% CIs provided for between-group comparisons. 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. There are no Tier 1 safety analyses in this study. No p-values would be provided for safety comparison.

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

The threshold of at least 4 events was chosen because the 95% 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, vital signs, and ECG parameters that are not pre-specified as Tier-1 endpoints will be considered Tier 3 safety parameters. Summary statistics for baseline, on-treatment, and change from baseline values will be provided by treatment group in table format. In addition, summary statistics for the difference between treatment groups will also be provided, along with nominal p-values for

between-group differences. Mean change from baseline over time will be plotted with the corresponding standard errors.

Detailed kinetics and characteristics of immune mediated adverse events occur in subjects treated with pembrolizumab will be summarized in the study.

Table 11 Analysis Strategy for Safety Parameters

Safety Tier	Safety Endpoint	p-Value	95% CI for Treatment Comparison	Descriptive Statistics
Tier 2	Any AE		X	X
	Any Grade 3-5 AE		X	X
	Any Serious AE		X	X
	Onset of First Grade 3-5 AE		X	X
	Any Drug-Related AE		X	X
	Any Serious and Drug-Related AE		X	X
	Any Grade3-5 and Drug-Related AE		X	X
	Dose Modification due to AE		X	X
	Discontinuation due to AE		X	X
	Death		X	X
	Specific AEs, SOCs (including ≥4 of subjects in one of the treatment groups)		X	X
Tier 3	Specific AEs, SOCs (incidence <4 of subjects in all of the treatment groups)			X
	Change from Baseline Results (Labs, ECGs, Vital Signs)			X

8.2.5.3 Summaries of Baseline Characteristics, Demographics, 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 reason for discontinuation will be displayed. Demographic variables (such as age) and baseline characteristics will be summarized by treatment either by descriptive statistics or categorical tables. The reasons for exclusion from the ITT population (if any) will be summarized.

8.2.6 Multiplicity

The overall type I error rate for this study is strictly controlled at 2.5% (one-sided). There are one planned analysis of ORR, one planned analysis of PFS and two planned analyses of OS. The ORR analysis will occur when the first 191 randomized subjects have a minimum of 6 months of follow up, and will be tested at the 0.5% (one-sided) alpha level. PFS will be tested only once at the planned PFS analysis after ~175 PFS events are observed, and will be tested at the 2.5% (one-sided) level if ORR is positive or at the 2.0% (one-sided) level if ORR is negative. OS will be tested only if PFS is positive and at the same level as PFS (i.e., step-down).

For OS, a Hwang-Shih-DeCani alpha-spending function with the gamma parameter -0.4 and beta-spending function with gamma -35 are constructed to implement group sequential boundaries that control the type I error rate as well as allow for non-binding futility analysis.

If at least 110 OS events are observed at the planned PFS analysis after ~175 PFS events are observed, an interim OS analysis will be conducted at the level determined by the spending function boundaries and the actual number of OS events at the PFS analysis time of the final PFS analysis. The final OS analysis will occur when ~170 OS events are observed at the level determined by the spending function and the actual number of OS events observed at the PFS analysis.

However, if there are less than 110 OS events at the planned PFS analysis, a nominal alpha of 0.01% (negligible impact on overall type I error rate) will be spent on the OS hypothesis at the time of the planned PFS analysis to prevent the study from premature stopping. The next interim and final OS analyses will be conducted after ~110 and ~170 OS events are observed, respectively, at the alpha level determined by the spending function boundaries and actual number of OS events

Following Amendment 08, the final OS analysis is no longer required and will not be performed as described above. This is due to the study hypothesis for OS being supported at the interim analysis with database cutoff of May 9, 2016.

8.2.7 Sample Size and Power Calculation

The study is event-driven and plans to randomize approximately 300 subjects with 1:1 ratio into the pembrolizumab arm and the SOC arm.

The planned ORR analysis will be conducted after first 191 subjects have a minimum of 6 months of follow up. This analysis has ~95% power to detect a 30% difference in ORR (e.g., 32% in SOC vs. 62% in pembrolizumab) at alpha=0.5%. An observed ORR difference of approximately 19% of an observed ORR difference is needed to achieve a positive ORR outcome (e.g., an observed ORR of approximately 32% in SOC versus 51% in pembrolizumab).

The planned PFS analysis will be conducted after approximately 175 PFS events are observed between the pembrolizumab arm and control. If there are less than 110 OS events at the time, the analysis may be delayed for up to 2 months or when the target OS number is reached, whichever occurs first. With ~175 PFS events, the study has ~98%/97% power to detect a HR 0.55 at alpha = 2.5%/2% (one-sided) at the PFS analysis. A p-value less than 2% (one-sided) for PFS approximately corresponds to an empirical HR of <0.744/0.738 (or approximately at least 7.4/7.5 months of median PFS in pembrolizumab vs. 5.5 months of median PFS in SOC). With ~110 OS events at the interim OS analysis, the study has ~90% power to demonstrate a numerically positive OS effect when the true HR is 0.7 assuming that half of the subjects in the control arm cross over to pembrolizumab at the time of analysis. The sample size calculation is based on the following assumptions: 1) PFS follows an exponential distribution with a median of 5.5 months in the control arm, 2) HR between

pembrolizumab and control is 0.55, 3) an enrollment period of 14 months and at least 6 months PFS follow-up after enrollment completion, and 4) a dropout rate of 10% per year. The assumption for the median PFS of 5.5 months in the control arm does not take into account potential prognostic implications in a biomarker selected population. As such, the control median may be more or less than 5.5 months.

The final OS analysis will be conducted after approximately 170 deaths have occurred between the pembrolizumab arm and control. The final OS analysis is expected to occur 14 months after enrollment completion. With 170 deaths at final OS analysis, the study has ~75% power to observe a HR <1 assuming that ~70% of the subjects in the control arm cross over to pembrolizumab. With two planned OS analyses, i.e., ~110 OS events at final PFS analysis and ~170 OS events at final OS analysis, the study has approximately 60%/57% power to detect a HR of 0.7 with the overall alpha controlled at 2.5%/2.0% (one-sided). However, due to the anticipated high crossover rate, the actual power could be substantially lower. A 95% CI will be provided for HR to characterize the OS effect in case superiority is not demonstrated. The details on the boundaries and nominal alpha levels at the final PFS and OS analyses are given in Section 8.2.9. The calculation is based on the following assumptions: 1) OS follows an exponential distribution with a median of 13 months in the control arm, 2) HR between pembrolizumab and control is 0.7, 3) an enrollment period of 14 months and 14-15 months follow-up after enrollment completion, and 4) a dropout rate of 0.005 per month. The assumption for the median OS of 13 months in the control arm does not take into account potential prognostic implications in a biomarker selected population. As such, the control median may be greater or less than 13 months.

Following Amendment 08, the final OS analysis is no longer required and will not be performed as described above. This is due to the study hypothesis for OS being supported at the interim analysis with database cutoff of May 9, 2016.The sample size and power calculation were performed in the software EAST and R (package “gsDesign”).

8.2.8 Subgroup Analyses and Effect of Baseline Factors

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

- Age category (≤65, >65 years)
- Sex (female, male)
- Race (white, non-white)
- ECOG status (0, 1)
- Geographic region of enrolling site (East Asia, non-East Asia)
- Histology (squamous, non-squamous)
- Smoking status (never, former, current)

- Brain metastasis status (baseline brain metastasis, no baseline brain metastasis)
- Investigators' choice of standard of care chemotherapy

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

8.2.9 ORR, PFS and OS analyses

One planned analysis of ORR, one planned analysis of PFS and two planned analyses of OS are currently planned. In this study, the futility bounds are non-binding, which means the bounds are considered guidance rather than strict bounds.

Following Amendment 08, only one analysis of OS is planned.

8.2.9.1 ORR, PFS analysis and interim OS analysis

The planned ORR analysis will take place when the first 191 subjects have at least 6 months of follow up, i.e., approximately 16 months after study start. ORR will be tested at alpha level of 0.5%. Only the first 191 subjects with at least 6 moths follow up will be included in the ORR analysis. An observed ORR difference of approximately 19% is needed to achieve a positive ORR outcome (e.g., an observed ORR of approximately 32% in SOC versus 51% in pembrolizumab). The trial will continue irrespective of the outcome.

The planned PFS analysis will take place when approximately 175 PFS events have been observed between the pembrolizumab arm and the control arm, which is expected to occur about 20 months after study start. If there are less than 110 OS events between two arms at the time, the analysis may be delayed for up to 2 months or until when the target OS number is reached, whichever occurs first. The primary objective of this analysis is to demonstrate superiority of pembrolizumab in PFS and exclude detrimental effect of pembrolizumab on OS.

The pembrolizumab arm will be compared to the SOC arm. An observed HR of ~0.738 or less would demonstrate PFS superiority at $\alpha = 2\%$ (one-sided) assuming ORR is negative at the first interim analysis, or an observed HR of ~0.744 or less if $\alpha = 2.5\%$ (one-sided) assuming ORR is positive at the first interim analysis. This HR approximately corresponds to at least 1.9-2.0 month improvement of the median PFS from 5.5 months in the SOC arm. The trial will be discontinued if the PFS superiority is not demonstrated.

The study will also examine OS at the planned PFS analysis. It is expected that approximately 110 deaths will be observed at this analysis. With ~110 OS events at the planned PFS analysis, the study has ~90% power to observe a HR <1 when the true HR on OS is 0.7, assuming that half of the subjects in the control arm cross over to pembrolizumab at the time of analysis. Via the group sequential approach with the predefined alpha-spending function (assuming that PFS is statistically significant), the superiority hypothesis will be tested at the type I error of 1.5% with ~110 deaths. An empirical HR < ~0.661, i.e., at least 6.7-month improvement in median OS, would demonstrate OS superiority. A futility analysis

will be conducted at the same time and an observed HR on OS >1.7 will approximately meet the criterion for futility. The boundaries for OS hypothesis testing will be re-calculated if actual monitoring schedule is altered.

However, if less than 110 OS events are observed at the planned PFS analysis, OS hypothesis will be tested at one-sided 0.01% level (negligible impact on overall type I error rate) to prevent premature stopping. For instance, with 80 OS events, an alpha level 0.01% approximately corresponds to an empirical HR of 0.44, i.e., 16.9-months improvement in median OS. A futility analysis will be conducted at level 0.01% at the same time and an observed HR on OS >2.3 will approximately meet the criterion for futility. The next OS interim analysis will then be conducted after ~110 OS events are observed with the boundaries calculated via the group sequential approach as presented in the previous paragraph.

8.2.9.2 Final OS Analysis

The final analysis will take place when approximately 170 deaths have occurred between the pembrolizumab arm and the SOC arm which is expected to occur approximately 28 months after study start.

Assuming PFS is statistically significant and the trial is not terminated at the interim OS analysis, the OS hypothesis at the final analysis will be tested at $\alpha = 1.65\%$. The empirical HR for OS superiority is < ~0.72, which corresponds to at least ~5-month improvement in median OS. The boundary for OS hypothesis testing will be re-calculated if actual monitoring schedule is altered. A 95% CI will be provided for HR to characterize the OS effect in case the superiority is not demonstrated. As an exploratory analysis, RPSFT model will be used to adjust for the crossover effect.

Following Amendment 08, the final OS analysis is no longer required and will not be performed as described in this section. This is due to the study hypothesis for OS being supported at the interim analysis with database cutoff of May 9, 2016.

8.2.10 Compliance (Medication Adherence)

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

8.2.11 Extent of Exposure

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

9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.1 Investigational Product

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

Clinical Supplies will be provided by the Sponsor as summarized in Table 12.

Table 12 Product Descriptions

Product Name & Potency	Dosage Form
Pembrolizumab (MK-3475) 25 mg / mL	Solution for infusion
Pemetrexed	Lyophilized powder for infusion
Paclitaxel 6 mg / mL	Solution for infusion
Carboplatin 10 mg / mL	Solution for infusion
Cisplatin 1 mg / mL	Solution for infusion
Gemcitabine	Lyophilized powder for infusion

The pemetrexed, paclitaxel, carboplatin, cisplatin and gemcitabine will be provided centrally by the Sponsor or locally by the trial site, subsidiary or designee, depending on local country operational or regulatory requirements. All other products will be provided locally by the trial site, subsidiary or designee.

The trial site will be responsible for recording the lot number, manufacturer and expiry date of any locally purchased product.

After the time of the marketing approval of pembrolizumab, “clinical trial drug” of pembrolizumab will be replaced with “post-marketing clinical trial drug”. The subjects can receive treatment of pembrolizumab as post-marketing clinical trial drug.

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 (MK-3475) will be provided as non-kitted single vials or as single vials in a kit box. The Pemetrexed will be supplied as a single vial. All other products will be provided as a kit with a single vial.

9.3 Clinical Supplies Disclosure

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

9.4 Storage and Handling Requirements

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

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

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

9.5 Returns and Reconciliation

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

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

9.6 Standard Policies

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

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

10.1 Confidentiality

10.1.1 Confidentiality of Data

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

10.1.2 Confidentiality of Subject Records

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

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

10.1.3 Confidentiality of Investigator Information

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

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

2. hospital or clinic address and telephone number;

3. curriculum vitae or other summary of qualifications and credentials; and

4. other professional documentation.

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

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

10.1.4 Confidentiality of IRB/IEC Information

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

10.2 Compliance with Financial Disclosure Requirements

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

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

10.3 Compliance with Law, Audit and Debarment

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

10.6 Data Management

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

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

10.7 Publications

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

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

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

Authorship credit should be based on 1) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; and 3) final approval of the version to be published. Authors must meet conditions 1, 2 and 3. Significant contributions to trial execution may also be taken into account to determine authorship, provided that contributions have also been made to all three of the preceding authorship criteria. Although

publication planning may begin before conducting the trial, final decisions on authorship and the order of authors' names will be made based on participation and actual contributions to the trial and writing, as discussed above. The first author is responsible for defending the integrity of the data, method(s) of data analysis and the scientific content of the manuscript.

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

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12.0 APPENDICES

12.1 Merck Code of Conduct for Clinical Trials

Merck*
Code of Conduct for Clinical Trials

I. Introduction

A. Purpose

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

B. Scope

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

II. Scientific Issues

A. Trial Conduct

1. Trial Design

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

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

2. Site Selection

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

3. Site Monitoring/Scientific Integrity

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

B. Publication and Authorship

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

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

III. Subject Protection

A. IRB/ERC review

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

B. Safety

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

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

C. Confidentiality

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

D. Genomic Research

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

IV. Financial Considerations

A. Payments to Investigators

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

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

B. Clinical Research Funding

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

C. Funding for Travel and Other Requests

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

V. Investigator Commitment

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

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

12.2 Collection and Management of Specimens for Future Biomedical Research

1. Definitions

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

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

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

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research

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

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

3. Summary of Procedures for Future Biomedical Research

a. Subjects for Enrollment

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

b. Informed Consent

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

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

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

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

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

c. eCRF Documentation for Future Biomedical Research Specimens

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

d. Future Biomedical Research Specimen Collections

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

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

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

4. Confidential Subject Information for Future Biomedical Research

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

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

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

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

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

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

5. Biorepository Specimen Usage

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

Analyses utilizing the Future Biomedical Research specimens may be performed by Merck, or an additional third party (e.g., a university investigator) designated by Merck. The investigator conducting the analysis will be provided with double coded specimens.

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

6. Withdrawal From Future Biomedical Research

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

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

7. Retention of Specimens

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

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

8. Data Security

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

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

9. Reporting of Future Biomedical Research Data to Subjects

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

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

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

10. Gender, Ethnicity and Minorities

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

11. Risks Versus Benefits of Future Biomedical Research

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

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

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

12. Self-Reported Ethnicity

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

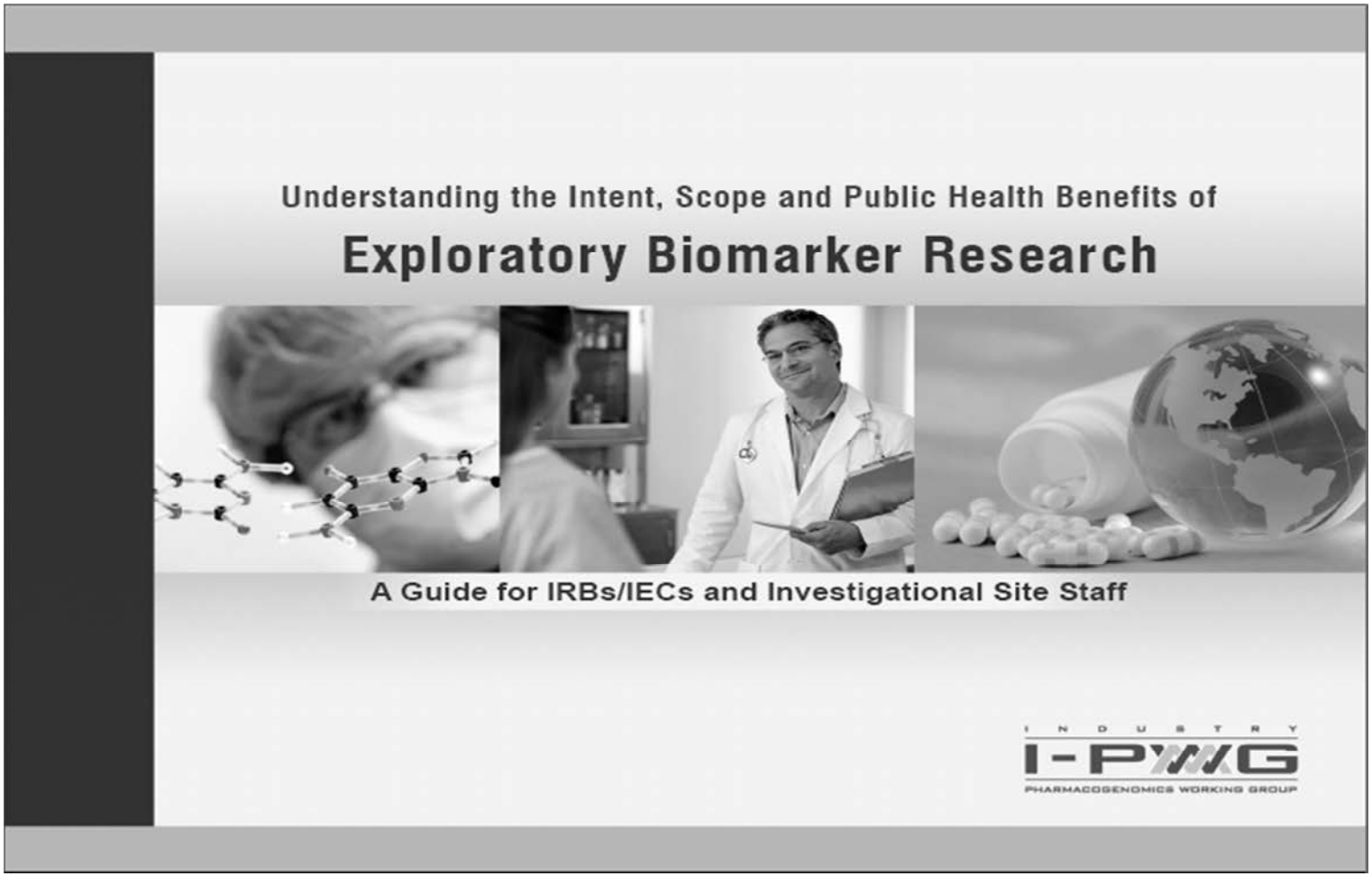
13. Questions

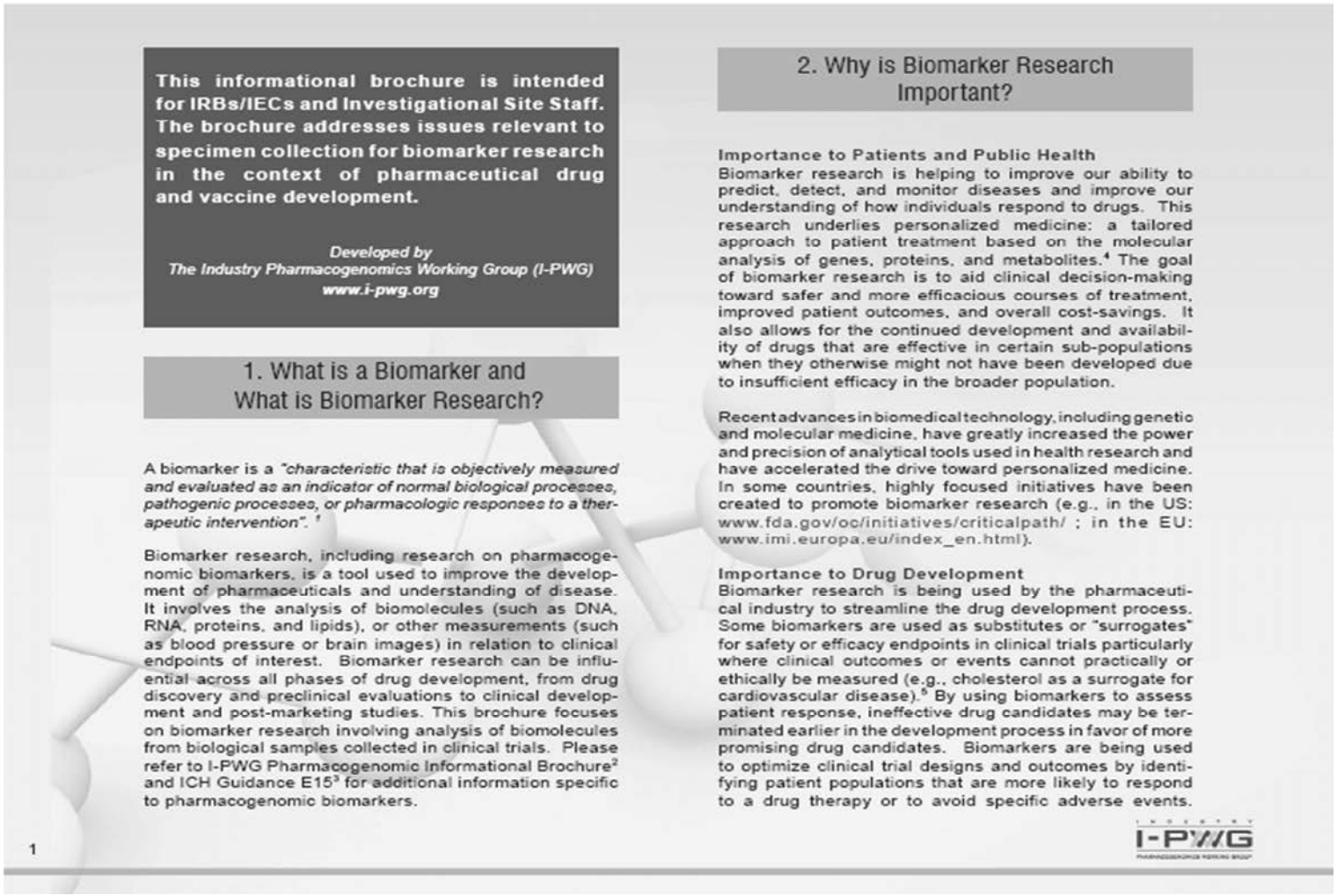
Any questions related to the future biomedical research should be e-mailed directly to clinical.specimen.management@merck.com.

14. References

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

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





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

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

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

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

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

2. Why is Biomarker Research Important?

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

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

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

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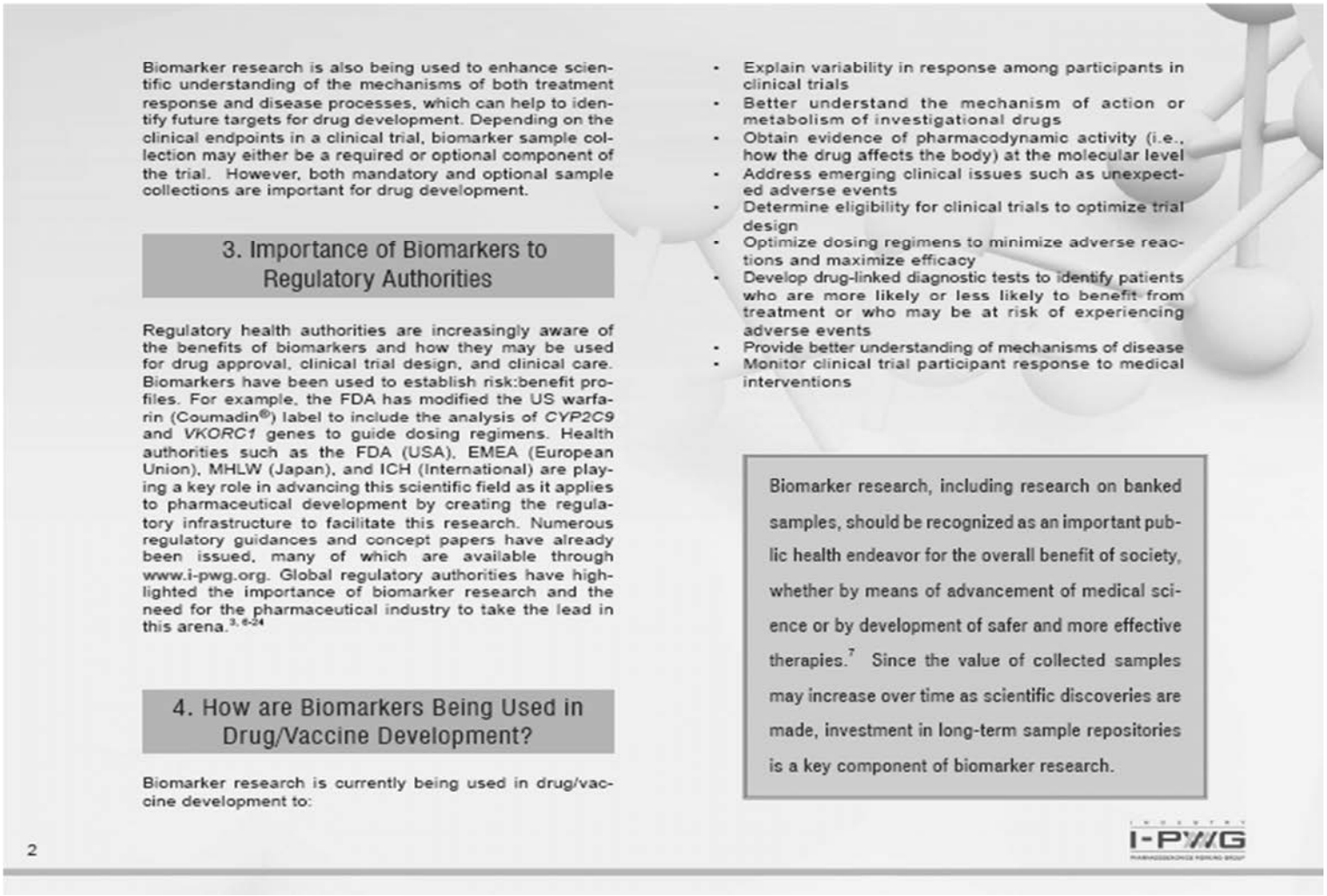

Biomarker research is also being used to enhance scientific understanding of the mechanisms of both treatment response and disease processes, which can help to identify future targets for drug development. Depending on the clinical endpoints in a clinical trial, biomarker sample collection may either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

3. Importance of Biomarkers to Regulatory Authorities

Regulatory health authorities are increasingly aware of the benefits of biomarkers and how they may be used for drug approval, clinical trial design, and clinical care. Biomarkers have been used to establish risk:benefit profiles. For example, the FDA has modified the US warfarin (Coumadin®) label to include the analysis of *CYP2C9* and *VKORC1* genes to guide dosing regimens. Health authorities such as the FDA (USA), EMEA (European Union), MHLW (Japan), and ICH (International) are playing a key role in advancing this scientific field as it applies to pharmaceutical development by creating the regulatory infrastructure to facilitate this research. Numerous regulatory guidances and concept papers have already been issued, many of which are available through www.i-pwg.org. Global regulatory authorities have highlighted the importance of biomarker research and the need for the pharmaceutical industry to take the lead in this arena.[3, 6-24]

4. How are Biomarkers Being Used in Drug/Vaccine Development?

Biomarker research is currently being used in drug/vaccine development to:

- Explain variability in response among participants in clinical trials
- Better understand the mechanism of action or metabolism of investigational drugs
- Obtain evidence of pharmacodynamic activity (i.e., how the drug affects the body) at the molecular level
- Address emerging clinical issues such as unexpected adverse events
- Determine eligibility for clinical trials to optimize trial design
- Optimize dosing regimens to minimize adverse reactions and maximize efficacy
- Develop drug-linked diagnostic tests to identify patients who are more likely or less likely to benefit from treatment or who may be at risk of experiencing adverse events
- Provide better understanding of mechanisms of disease
- Monitor clinical trial participant response to medical interventions

Biomarker research, including research on banked samples, should be recognized as an important public health endeavor for the overall benefit of society, whether by means of advancement of medical science or by development of safer and more effective therapies.[7] Since the value of collected samples may increase over time as scientific discoveries are made, investment in long-term sample repositories is a key component of biomarker research.

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5. Biomarkers are Already a Reality in Health Care

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

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

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

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

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

6. Biomarker Samples from Clinical Trials: An Invaluable Resource

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

7. Informed Consent for Collection & Banking of Biomarker Samples

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

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

Optional vs. Required Subject Participation

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

Consent for Future Research Use

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

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

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

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

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

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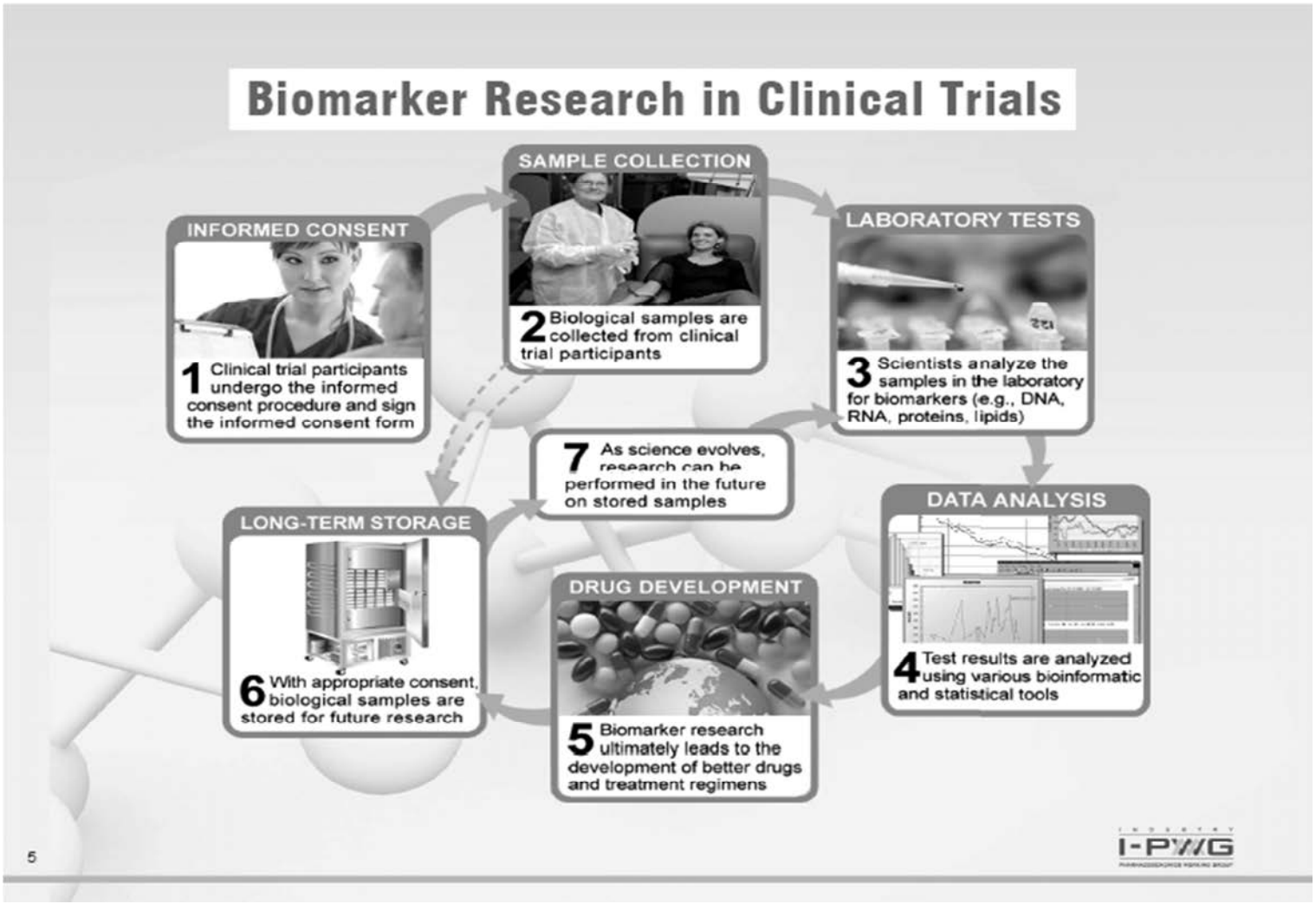
Biomarker Research in Clinical Trials
SAMPLE COLLECTION
2 Biological samples are collected from clinical trial participants
LABORATORY TESTS
3 Scientists analyze the samples in the laboratory for biomarkers (e.g., DNA, RNA, proteins, lipids)
INFORMED CONSENT
1 Clinical trial participants undergo the 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
LONG-TERM STORAGE
6 With appropriate consent, biological samples are stored for future research
DRUG DEVELOPMENT
4 Test results are analyzed using various bioinformatic and statistical tools
5 Biomarker research ultimately leads to the development of better drugs and treatment regimens
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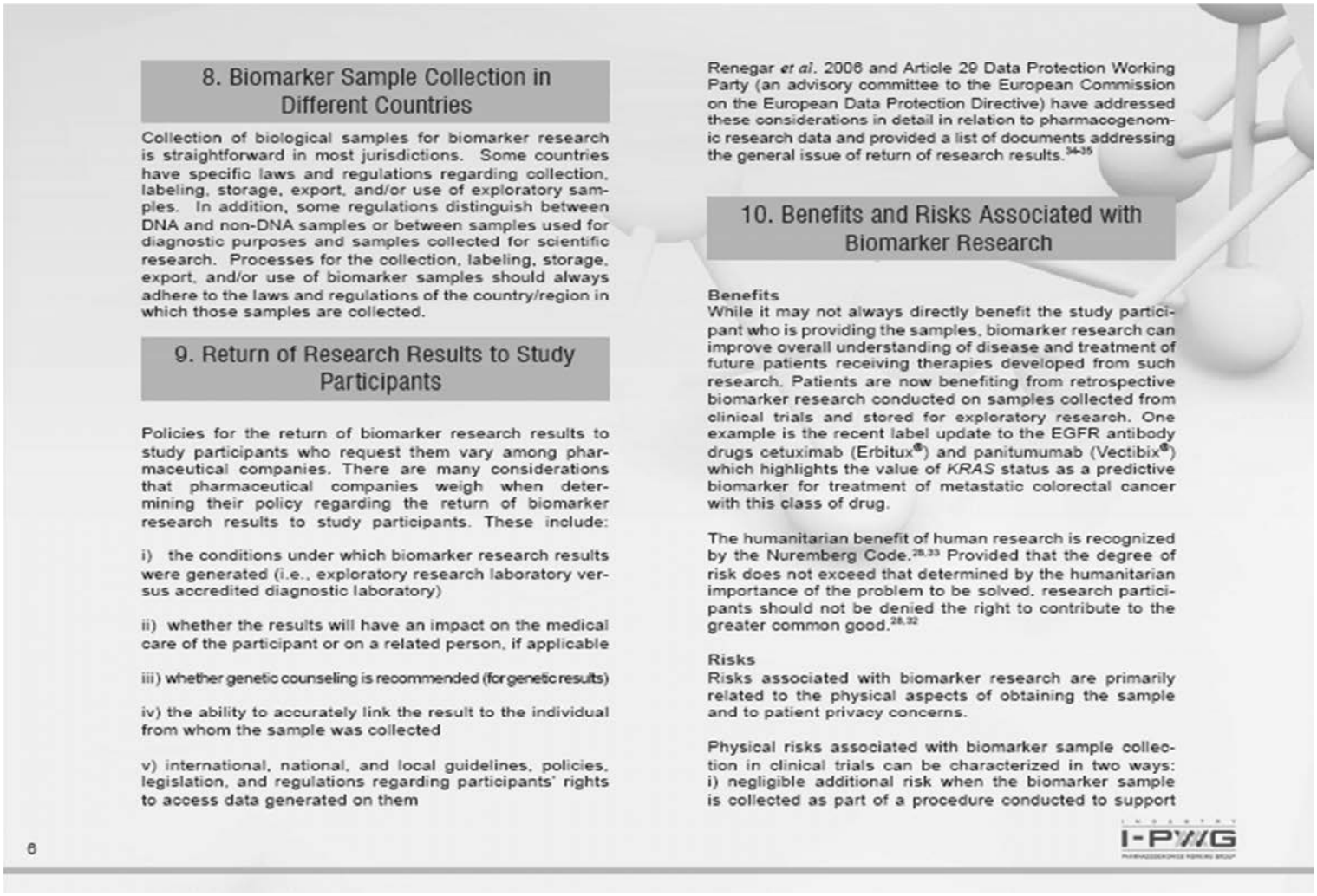

8. Biomarker Sample Collection in Different Countries

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*. 2008 and Article 29 Data Protection Working Party (an advisory committee to the European Commission on the European Data Protection Directive) have addressed these considerations in detail in relation to pharmacogenomic research data and provided a list of documents addressing the general issue of return of research results.[34-35]

10. Benefits and Risks Associated with Biomarker Research

Benefits

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

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

Risks

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

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

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

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

11. Privacy, Confidentiality, and Patient Rights

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

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

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

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

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

12.Where to Get More Information?

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

13. What is I-PWG?

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

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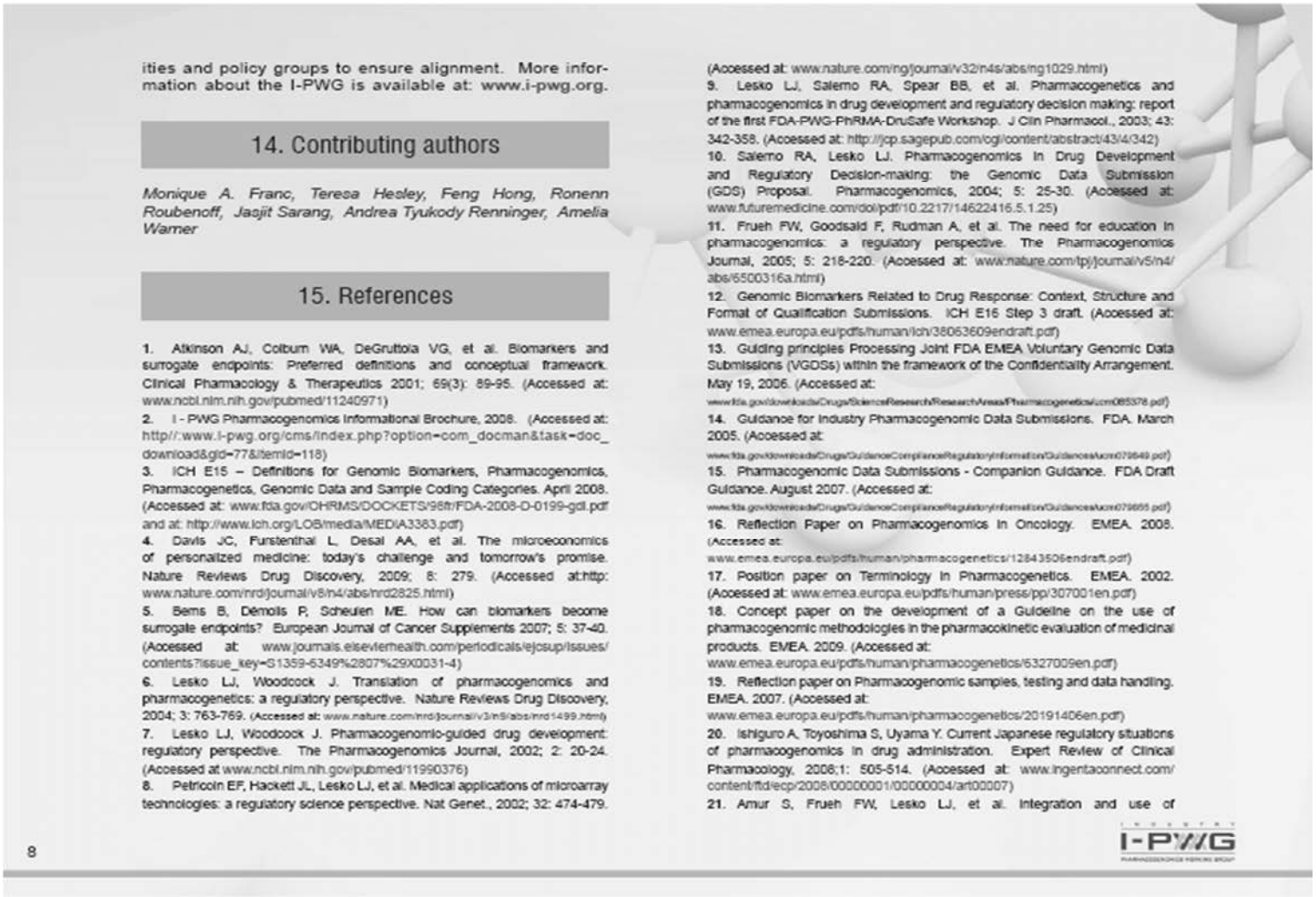

ities and policy groups to ensure alignment. More information about the I-PWG is available at: www.i-pwg.org.

14. Contributing authors

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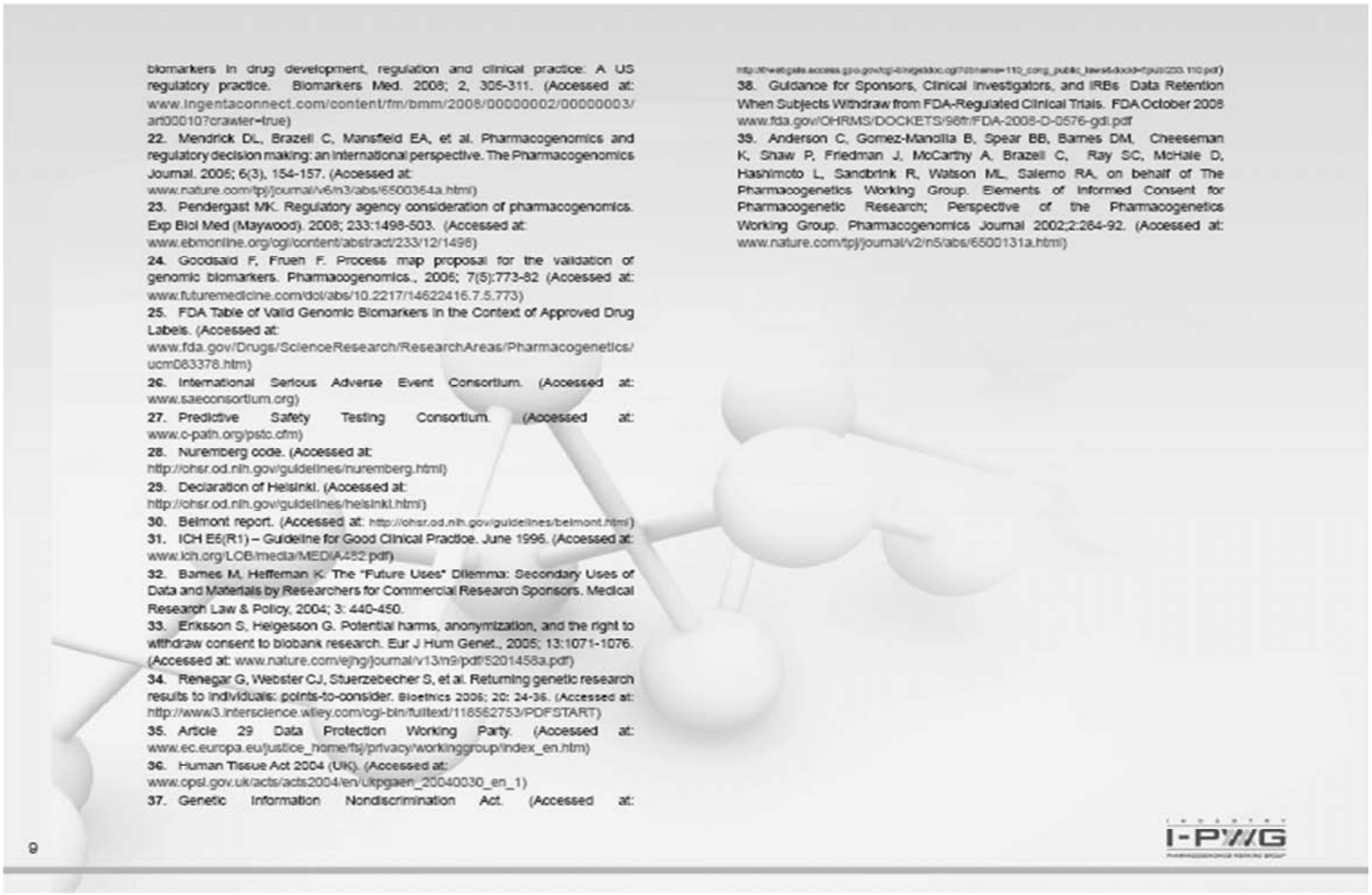

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12.4 List of Abbreviations

Abbreviation/Term	Definition
1L	First Line
AE	Adverse event
ADA	Anti-Drug Antibodies
ALT	Alanine aminotransferase
ALK	anaplastic lymphoma kinase
ANC	Absolute neutrophil count
aPTT	Activated partial thromboplastin time
AUC	Area Under Curve
AST	Aspartate aminotransferase
β-HCG	Beta human chorionic gonadotropin
BSC	best supportive care
CBC	Complete blood count
CI	confidence interval
CNS	Central nervous system
CR	Complete response
CrCl	Calculated creatinine clearance
CRF	Case report form
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Toxicity Criteria for Adverse Events
DLT	Dose Limiting Toxicity
DNA	Deoxyribonucleic acid
DMC	Data Monitoring Committee DMC
EBUS	Endobronchial Ultrasound
ECI	Events of clinical interest
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EGFR	epidermal growth factor receptor
EMA	European Medicines Agency
ERC	Ethics review committee
FBR	Future Biomedical Research
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
Hb	Hemoglobin
HBV	Hepatitis B
HCV	Hepatitis C
HIV	Human immunodeficiency virus
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Conference on Harmonization
IHC	Immunohistochemistry
irRC	immune-related response criteria
INR	International normalized ratio
irAEs	Immune-related adverse events
IRB	Institutional Review Board
ITT	intent-to-treat
IV	Intravenous
Kg	Kilogram
LDH	lactate dehydrogenase
mcL	Millimeters
MEL	Melanoma
MG	Milligram
Mg/kg	Milligram per kilogram

Abbreviation/Term	Definition
MRI	Magnetic resonance imaging
MSD	Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
MTD	Maximum tolerated dose
NA or N/A	Not Applicable
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NSCLC	non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival
OTC	Over-the-counter
PD	Progressive disease
PD-L1	Programmed Cell Death Ligand 1
PD-L2	Programmed Cell Death Ligand 2
PET	Positron emission tomography
PFS	Progression free survival
PFS2	next line of therapy PFS2
PGt	Pharmacogenetic
PK	Pharmacokinetic
PK-PD	Pharmacokinetic-Pharmacodynamic
PRO	patient reported outcome
PR	Partial response
PT	Prothrombin time
Q-TWiST	Quality-adjusted Time without Symptoms or Toxicity
RCC	renal cell carcinoma
RNA	Ribonucleic acid
RECIST	Response Evaluation Criteria in Solid Tumors RECIST 1.1
RR	Response rate
Q3W	Every 3 weeks
SAE	Serious adverse events
SAP	Statistical Analysis Plan
SFU	Survival follow-up
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SOC	Standard of Care
TIL	Tumor-infiltrating lymphocytes
TKI	tyrosine kinase inhibitors
TSH	Thyroid stimulating hormone
TTP	Time To Progression
ULN	Upper limit of normal
WHO	World Health Organization

12.5 ECOG Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.
* As published in Am J Clin Oncol: *Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5:649-55.* Eastern Cooperative Oncology Group, Robert Comis MD, Group Chair.	

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

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

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

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

* As published in the European Journal of Cancer:

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

12.8 Immune Related Response Criteria

For all subjects who experience disease progression on study, the date noted for of disease progression is the time of the scan where it is originally detected, and not the following date of the confirmatory scan.

Definitions of measurable and non-measurable disease

Measurable disease: Neoplastic masses that can be precisely measured in 2 in-plane perpendicular diameters. Both its longest diameter and its longest perpendicular must be greater than or equal to 10 mm or 2 times the axial slice thickness. Lymph nodes must have a short-axis line-length of ≥ 15 mm. Malignant lymph nodes must be measurable in 2 perpendicular diameters. Both its longest diameter and its longest perpendicular must be greater than or equal to 15 mm or 2 times the axial slice thickness. The quantitative endpoint will be defined as the product of the longest diameter with its longest perpendicular.

Non-measurable disease: Non-measurable lesions are those that are not suitable for quantitative assessment over time. These include:

1) Neoplastic masses that are too small to measure, because their longest uninterrupted diameter or longest perpendicular are less than 10 mm or two times the axial slice thickness.

2) Neoplastic masses whose boundaries cannot be distinguished. This includes masses which cannot be demarcated from surrounding tissue because of inadequate contrast, masses with overly complex morphology, or those with highly heterogeneous tissue composition.

3) Other types of lesions that are confidently felt to represent neoplastic tissue, but difficult to quantify in a reproducible manner. These include bone metastases, leptomeningeal metastases, malignant ascites, pleural/pericardial effusions, inflammatory breast disease, lymphangitis cutis/pulmonis, cystic lesions, ill-defined abdominal masses, etc.

For irRC, only target lesions selected at baseline and measurable new lesions are taken into account.

At the baseline tumor assessment, the sum of the products of the two largest perpendicular diameters (SPD) of all **index lesions** (five lesions per organ, up to 10 visceral lesions and five cutaneous index lesions) is calculated.

At each subsequent tumor assessment, the SPD of the index lesions and of new, measurable lesions (≥ 5 X 5 mm; up to 5 new lesions per organ: 5 new cutaneous lesions and 10 visceral lesions) are added together to provide the total time-point **tumor burden.**

Overall response using irRC:

- **Complete Response (irCR):** Complete disappearance of all tumor lesions (whether measureable or not, and no new lesions). CR must be confirmed by repeated, consecutive assessments made no less than 4 weeks from the date first documented.

- **Partial Response (irPR):** Decrease in SPD of 50% or greater by a consecutive assessment at least 4 weeks after first documentation.

- **Stable Disease (irSD):** Failure to meet criteria for irCR or irPR, in absence of irPD.

- **Progressive Disease (irPD):** At least 25% increase in SPD relative to nadir (minimum recorded tumor burden) Confirmation by a repeat, consecutive assessment no less than 4 weeks from the data first documented.

Please note other key differences between irRC and the original WHO criteria:

New measurable lesions will be incorporated into the SPD

New non measurable lesions do not define progression but preclude irCR

Non-index lesions contribute to defining irCR (complete disappearance required).

See the Site Imaging Manual for more details.

REFERENCE

IrRC for the current protocol is adopted from the following reference:

Wolchok JD, Hoos A, O'Day S et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. Clinical Cancer Research 2009 Dec 1;15(23):7412-20. Epub 2009 Nov 24.

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

TYPED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	