Official Protocol Title:	A Phase 3 Randomized, Double-Blind, Placebo-controlled Trial of Pembrolizumab (MK-3475/SCH900475) in Combination with Etoposide/Platinum (Cisplatin or Carboplatin) for the First-line Treatment of Subjects with Extensive Stage Small Cell Lung Cancer(KEYNOTE-604)
NCT number:	NCT03066778
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(hereafter referred to as the Sponsor or Merck)
One Merck Drive
P.O. Box 100
Whitehouse Station, New Jersey, 08889-0100, U.S.A.

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

TITLE:

A Phase 3 Randomized, Double-Blind, Placebo-controlled Trial of Pembrolizumab (MK-3475/SCH900475) in Combination with Etoposide/Platinum (Cisplatin or Carboplatin) for the First-line Treatment of Subjects with Extensive Stage Small Cell Lung Cancer (KEYNOTE-604)

IND NUMBER: 116833

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DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Original protocol	15 DEC-2016	
Amendment 01	21-DEC-2016	Corrected a typographical error in the numbering of the inclusion criteria so that the structure of the trial database and the electronic data capture forms can be created correctly.
Amendment 02	23-FEB-2017	Corrected the wording of exclusion criterion #5, which stated the opposite of what was intended and to provide more detail and clarity where needed.
Amendment 03	10-APR-2017	Removed the option to cross over from the etoposide/platinum/saline placebo arm to pembrolizumab treatment to improve the interpretation of the long-term benefit.
Amendment 04	02-JUN-2017	Removed the requirement for unblinding treatment assignment after documentation of progressive disease (PD) because the option to cross over to pembrolizumab was removed and, with it, the need to unblind.
Amendment 05	01-SEP-2017	Clarified exclusion criterion #4 regarding brain metastases to ensure that no subjects with brain metastases are enrolled in the study.
Amendment 06	30-NOV-2017	Updated the dose modification guidelines for pembrolizumab to include information regarding the treatment of myocarditis; revised the requirements for survival follow-up to allow for more frequent data collection; added a Day 8 visit during Cycles 1 through 4 to allow for more frequent safety monitoring.

Document	Date of Issue	Overall Rationale
Amendment 07	03-OCT-2018	[redacted]; changed the alpha allocation between the primary (overall survival [OS] and PFS) and key secondary (objective response rate [ORR]) hypothesis on the basis of accumulating external data on PFS and OS in immunotherapy-chemotherapy combinations in small cell lung cancer to allow more alpha to be allocated to the primary endpoints.
Amendment 08	07-DEC-2018	[redacted] the assumption for median PFS in the control arm was changed to 4.3 months based on external data published from other clinical trials; and the power and efficacy bound calculations were updated to reflect the change in PFS median assumption and an alpha spending approach.
Amendment 09	23-APR-2019	Updated criteria for the final OS analysis to be a minimum of 294 events, or 31 months from study start, whichever occurs later to ensure sufficient follow-up time for the final OS analysis. Added clarification to describe the alpha-spending strategy for PFS and OS in detail. Corrected a publishing error in Amendment 08.

SUMMARY OF CHANGES

PRIMARY REASON(S) FOR THIS AMENDMENT:

Section Number	Section Title	Description of Change(s)	Rationale
8.7	Interim Analyses	The final analysis timing was updated as follows: "The final OS analysis is planned when a minimum of 294 deaths have been observed or approximately 31 months after first subject enrolled, whichever occurs later."	By allowing the final OS analysis to occur after a minimum of 294 events have been observed or approximately 31 months after the first subject is enrolled, whichever occurs later, the trial ensures adequate follow-up time for the final OS analysis.
8.8	Multiplicity	Added the following statements to describe the alpha-spending strategy for PFS and OS in detail: "The alpha spending at each interim analysis is determined using a Lan-DeMets O'Brien-Fleming spending function, and the information fraction (ratio of the actual number of events at the interim analysis relative to a targeted 294 events at the final analysis). The final analysis will use the remaining Type I error not spent at earlier analyses, regardless of the number of events observed at the final analysis. The p-value bounds at second interim and final analysis will be calculated by considering the correlation between the test statistics as determined by the actual number of OS events at the previous and current analysis."	To clarify that the alpha spending is event based, and not subjected to change, if the actual number of events at the final analysis exceeds the targeted number of events at final analysis.

ADDITIONAL CHANGE(S) FOR THIS AMENDMENT:

Section Number	Section Title	Description of Change(s)	Rationale
11.0	List of References	Included all references cited in the text of the protocol.	Due to a publishing error, the list of references in protocol Section 11.0 was truncated when Amendment 08 was finalized. Therefore, it is being updated here.

1.0 TRIAL SUMMARY

Abbreviated Title	Phase 3 trial of first line etoposide/platinum (EP) with or without pembrolizumab in ES-SCLC (KEYNOTE-604)
Sponsor Product Identifiers	MK-3475 Pembrolizumab
Trial Phase	III
Clinical Indication	First-line treatment of extensive stage small cell lung cancer (ES-SCLC) in combination with standard of care (SOC) chemotherapy
Trial Type	Interventional
Type of control	Placebo
Route of administration	Intravenous (IV)
Trial Blinding	Double-blind
Treatment Groups	Arm 1: Pembrolizumab + EP: Pembrolizumab 200 mg IV every 3 weeks (Q3W) on Day 1 Etoposide 100 mg/m^2 IV Q3W on Days 1, 2, and 3 Platinum, investigator's choice Carboplatin titrated to an area under the plasma drug concentration-time curve (AUC) of 5 IV Q3W on Day 1 OR Cisplatin 75 mg/m^2 IV Q3W on Day 1 Arm 2: Placebo + EP: Placebo IV Q3W on Day 1 Etoposide 100 mg/m^2 IV Q3W on Days 1, 2, and 3 Platinum, investigator's choice Carboplatin titrated to an AUC of 5 IV Q3W on Day 1 OR Cisplatin 75 mg/m^2 IV Q3W on Day 1
Number of trial subjects	Approximately 430 subjects will be enrolled.
Estimated duration of trial	The Sponsor estimates that the trial will require approximately 4.5 years from the time the first subject signs the informed consent until the last subject's last study-related phone call or visit.
Duration of Participation	Each subject will participate in the trial from the time the subject signs the informed consent form through the final protocol-specified contact. After a screening phase of up to 28 days, each subject will be randomized to receive trial treatment (pembrolizumab + EP or placebo + EP). The SOC treatment component (EP) will be given for the first 4 cycles with pembrolizumab or placebo, after which partial and complete responders may receive prophylactic cranial irradiation at the discretion of the investigator. Treatment with pembrolizumab or placebo will continue until a total of 35 cycles of treatment have been administered or until one of the treatment discontinuation criteria occurs: confirmed disease progression, unacceptable adverse event(s) (AEs), intercurrent illness,

	investigator decision to withdraw the subject, noncompliance, or administrative reasons requiring cessation of treatment. Subjects who experience documented progressive disease (PD) verified by blinded independent central review will have the option to remain on study and continue receiving the originally assigned trial treatment for a total of 35 cycles at the discretion of the investigator (Section 7.1.5.5). Subjects who stop trial treatment after receiving 35 administrations of trial treatment for reasons other than PD or intolerability may be eligible for the Second Course Phase, up to 17 additional administrations of pembrolizumab (approximately 1 year), upon experiencing disease progression (Section 7.1.5.4). Subjects in the saline placebo arm are not eligible for the Second Course Phase. After the end of treatment, each subject will be followed for the occurrence of AEs and spontaneously reported pregnancy (Section 7.2). Subjects who discontinue for reasons other than PD will have post-treatment follow-up for disease status until experiencing PD confirmed by the site per immune-related Response Evaluation Criteria in Solid Tumors (irRECIST) or per RECIST version 1.1 (modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ) as assessed by BICR, initiating a non-study cancer treatment, withdrawing consent, or becoming lost to follow-up. All subjects will be followed by telephone for overall survival until death, withdrawal of consent, or the end of the study.

Randomization Ratio	1:1

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

2.0 TRIAL DESIGN

2.1 Trial Design

This is a worldwide, randomized, placebo-controlled, Phase 3, parallel group, multi-site, double-blind trial of pembrolizumab plus standard of care (SOC) chemotherapy (EP) in subjects with ES-SCLC who have not previously received systemic therapy for this malignancy.

Approximately 430 subjects will be randomized (1:1) to either pembrolizumab + EP or placebo + EP. Randomization will be stratified by type of platinum therapy (cisplatin or carboplatin), Eastern Cooperative Oncology Group (ECOG) performance status score (0 or 1), and lactate dehydrogenase (LDH) measurement (≤ or > upper limit of normal [ULN]) at baseline. Positive tumor programmed cell death-ligand 1 (PD-L1) expression will not be required for enrollment; however, subjects' tumors will be screened for PD-L1 expression. An overview of the trial design is depicted in Figure 1.

Prior to randomization, the investigator will determine whether the subject will receive cisplatin or carboplatin. Subjects are allowed to switch from cisplatin to carboplatin if the

subject develops an adverse event (AE), becomes ineligible for further cisplatin therapy, and/or the investigator considers switching to carboplatin to be in the best interest of the subject.

During the Treatment Phase, subjects will have a study visit every 3 weeks (Q3W) for assessments and trial treatment administration. In Cycles 1 to 4, subjects will receive the SOC treatment component (EP) along with either pembrolizumab 200 mg or placebo. Subjects in either treatment arm who achieve a partial response (PR) or complete response (CR) at the completion of Cycle 4 may be offered prophylactic cranial irradiation (PCI) at the discretion of the investigator (Section 7.1.2.6). Treatment with PCI should begin within 2 to 4 weeks (no later than 6 weeks) after the last trial treatment in Cycle 4. Trial treatment may continue during PCI; however, if it is necessary to suspend trial treatment, it must be restarted no later than 2 weeks after completion of PCI. Subjects will continue to receive treatment with pembrolizumab or placebo Q3W for up to an additional 31 cycles (up to 35 cycles total) or until occurrence of one or more treatment discontinuation criteria: disease progression as assessed by blinded independent central review (BICR) confirmed per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) (modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ), intolerable toxicity or unacceptable AEs, intercurrent illness that prevents further administration of treatment, investigator decision to withdraw the subject, noncompliance with trial treatment or procedure requirements, or administrative reasons requiring cessation of treatment.

After randomization, subjects will be evaluated with radiographic imaging to assess response to treatment; treatment-based decisions should be made by the investigator based on immune-related RECIST (irRECIST) (Section 4.2.3.5). All imaging obtained on study will be submitted for BICR using RECIST 1.1 for verification of progressive disease (PD) and for determination of objective response rate (ORR) and progression-free survival (PFS). Adverse event monitoring will be ongoing throughout the trial and AEs will be graded for severity according to the guidelines outlined in the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events version 4.0 (CTCAE 4.0).

After verification of PD as assessed by BICR per RECIST 1.1 (modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ), subjects will have the option to remain on study and continue receiving the originally assigned trial treatment for a total of 35 cycles at the discretion of the investigator, provided they are deemed to be benefiting and are clinically stable (Section 7.1.2.7.6). Alternatively, subjects may choose to receive treatment with an appropriate second-line (2L) therapy as determined by the investigator.

At the discretion of the investigator and in consultation with the Sponsor, subjects assigned to the pembrolizumab arm who complete 35 treatment administrations may be eligible for retreatment with open-label pembrolizumab monotherapy at the time of radiographic disease progression (verified by BICR), provided that no other systemic therapy for SCLC has been administered. This retreatment is called the Second Course Phase (Section 6.2 and Section 7.1.5.5). Subjects in the saline placebo arm are not eligible for the Second Course Phase. Treatment assignment will be unblinded for those subjects who meet all criteria for

the Second Course Phase. Response or progression during the Second Course Phase will not be included in the analyses of the ORR or PFS endpoints in this trial.

After the end of treatment, each subject will be followed for a minimum of 30 days for AE monitoring even if the subject started non-study antineoplastic treatment. Serious adverse events (SAEs) will be documented for up to 90 days following cessation of the Sponsor's product, or 30 days following cessation of treatment if the subject initiates non-study cancer treatment, whichever is earlier. After this period, any SAEs considered to be related to the trial treatment must be reported. Subjects will have post-treatment follow-up for disease status, until initiating a non-study cancer treatment, experiencing disease progression or death, withdrawing consent, or becoming lost to follow-up. After documented disease progression or the start of non-study cancer treatment, subjects will have contact with study personnel by telephone until death, withdrawing consent, or becoming lost to follow-up. The Sponsor may request survival status to be assessed at additional time points and entered into the database during the course of the trial. For example, survival status may be requested prior to, but not limited to, external Data Monitoring Committee (DMC) reviews, as well as at interim and/or final analyses.

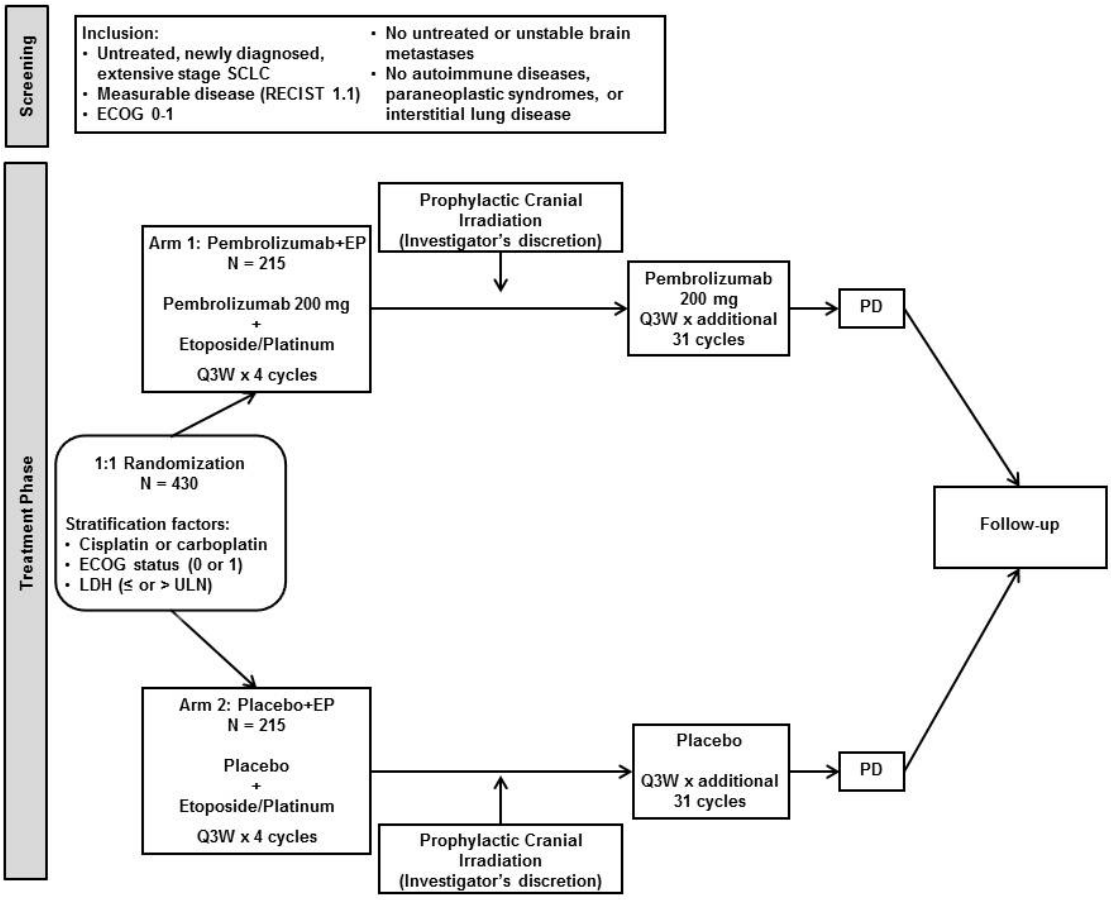
This trial has dual primary endpoints: 1) PFS as assessed by BICR per RECIST 1.1 modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ and 2) overall survival (OS). Trial results will be considered positive if the hypothesis test for either one of these primary endpoints is successful. Efficacy also will be evaluated using ORR (key secondary endpoint) and duration of response (duration of response [DOR]; secondary endpoint) as assessed by BICR per RECIST 1.1 modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ (Details are provided in the Site Imaging Manual).

Safety will be assessed using NCI CTCAE 4.0 and is a secondary endpoint. Quality of life assessments encompass both secondary and exploratory endpoints. Additional exploratory analyses will include: PFS using investigator-assessed irRECIST; ORR using investigator-assessed irRECIST; DOR using investigator-assessed irRECIST; PFS, OS, and ORR in PD-L1 subgroups; and identification of additional biomarkers of response.

Two interim efficacy analyses and 1 final analysis are planned in this study. This trial will use a group sequential design based on pre-specified criteria, using an independent, external DMC to monitor safety and efficacy results. Details are described in Section 8.0.

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

2.2 Trial Diagram



Abbreviations: ECOG=Eastern Cooperative Oncology Group, EP=etoposide / platinum, LDH=lactate dehydrogenase, PD=progressive disease, PFS=progression-free survival, Q3W=every 3 weeks, RECIST 1.1=Response Evaluation Criteria in Solid Tumors version 1.1, SCLC=small cell lung cancer, ULN=upper limit of normal

See Study Flow Chart (Section 6.2) for details regarding Second Course Phase

Figure 1 Trial Design Overview

3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

To accomplish the objectives listed below, pembrolizumab + EP will be compared with placebo + EP for the treatment of subjects with newly diagnosed ES-SCLC.

3.1 Primary Objective(s) & Hypothesis(es)

1) **Objective:** To evaluate PFS as assessed by BICR per RECIST 1.1 modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ.

   Hypothesis (H1): Pembrolizumab + EP prolongs PFS per RECIST 1.1 by BICR compared with placebo + EP.

2) **Objective:** To evaluate OS.

   Hypothesis (H2): Pembrolizumab + EP prolongs OS compared with placebo + EP.

The study is considered to have met its objective if the pembrolizumab + EP arm is superior to placebo + EP in PFS or OS.

3.2 Secondary Objective(s) & Hypothesis(es)

1) **Objective**: To evaluate ORR as assessed by BICR per RECIST 1.1 modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ.

   Hypothesis: Pembrolizumab + EP improves ORR per RECIST 1.1 by BICR compared to placebo + EP.

2) **Objective**: To evaluate DOR as assessed by BICR per RECIST 1.1 modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ.

3) **Objective:** To evaluate the safety profile in each treatment arm using NCI CTCAE 4.0.

4) **Objective:** To evaluate the following patient-reported outcomes (PROs):

   - Mean change from baseline at Week 18 in global health status/quality of life using the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) global health status/quality of life scale. If the overall PRO completion or compliance rates at Week 18 are less than 60% or 80%, respectively, then the primary analysis time point will be moved to the next earliest time point in which the rates are at least 60% for completion and at least 80% for compliance.

   - Time to true deterioration in the composite endpoint of cough, chest pain, and dyspnea using the EORTC QLQ-C30 and Lung Cancer Module 13 (QLQ-LC13).

3.3 Exploratory Objectives

1) Objective: To evaluate changes in health-related quality of life assessments from baseline using the EORTC QLQ-C30 and EORTC QLQ-LC13.

2) Objective: To characterize utilities using the European Quality of Life Five-dimension Five-level Scale Questionnaire (EQ-5D-5L).

3) Objective: To evaluate ORR, PFS, and DOR per irRECIST as assessed by the investigator.

4) Objective: To evaluate ORR and PFS as assessed by BICR per RECIST 1.1 modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ, and OS by PD-L1 expression (tumor proportion score [TPS] <1% versus ≥1%, combined positive score [CPS] <1 versus ≥1).

5) Objective: To evaluate the relationship between deoxyribonucleic acid (DNA) mutational burden and ribonucleic acid (RNA) immune signatures analyses and clinical outcome.

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

4.0 BACKGROUND & RATIONALE

4.1 Background

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

4.1.1 Pharmaceutical and Therapeutic Background

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

The programmed cell death protein-1 (PD-1) receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on

the cell surface of activated T cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. The PD-1 receptor (encoded by the gene Pdcd1) is an immunoglobulin (Ig) superfamily member related to CD28 and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and 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 [34] [42]. The PD-1 receptor was shown to be expressed on activated lymphocytes, including peripheral CD4+ and CD8+ T-cells, B-cells, regulatory T cells, 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 ligand to PD-1 inhibits T-cell activation triggered through the T-cell receptor. Expression of PD-L1 occurs at low levels on various non hematopoietic tissues, most notably on vascular endothelium, whereas expression of the PD L2 protein is only detectable on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments. Immune T-cell activation in lymphoid organs is thought to be controlled by PD-L2, 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 shown to express abundant levels of this T-cell inhibitor. High expression of PD-L1 on tumor cells (and to a lesser extent, expression of PD-L2) has been found to correlate with poor prognosis and survival in various cancer types, including renal cell [48], pancreatic [49], hepatocellular [50], and ovarian [51]. Furthermore, PD-1 may also regulate tumor-specific T-cell expansion in subjects with melanoma [52]. The prognostic implications of PD-L1 expression in advanced tumors are being investigated further in ongoing epidemiologic studies.

Because the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion, it is an attractive target for therapeutic intervention. Pembrolizumab is a potent and highly selective humanized monoclonal antibody of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, preventing attenuation of the immune system. Pembrolizumab clinical trials are ongoing in a number of advanced cancer types, including melanoma, non-small cell lung cancer (NSCLC), head and neck cancer, urothelial cancer, triple-negative breast cancer, gastric cancer, and hematologic malignancies. For study details, refer to the IB.

4.1.2 Information on Other Trial-related Therapy

4.1.2.1 Etoposide/Platinum Therapy

Standard first-line (1L) treatment for the vast majority of patients with SCLC, regardless of stage, involves combination chemotherapy with etoposide plus cisplatin or carboplatin.

The etoposide/cisplatin regimen was tested in SCLC because this combination produced synergistic activity in preclinical systems. In addition, both agents could be given at full doses because of less myelosuppression with cisplatin. The first report of demonstrated

activity with the combination dates back to 1979 [53]. Subsequent randomized trials compared etoposide/cisplatin to cyclophosphamide, vincristine, and an anthracycline [54] [55] [56]. Less myelosuppression occurred with etoposide/cisplatin, and, when given with radiation, patients experienced less esophagitis and interstitial pneumonitis. Retrospective analyses and meta-analyses also support the superiority of a cisplatin- or carboplatin-containing regimen for SCLC [57] [58] [59]. As a result, EP is now the standard 1L chemotherapy regimen for SCLC. Several randomized studies evaluating etoposide and cisplatin compared with other regimens have shown consistent results for this doublet with response rates of 45% to 60%, median time to progression of 5 months, and median OS of 10 months [60] [61]. Notably, emerging data from recent global trials evaluating novel treatments in SCLC demonstrated a lower median PFS of approximately 4.3 to 4.4 months in the EP control arm, yet median OS remains consistent at approximately 10.3 to 10.9 months [62] [63].

Carboplatin has been substituted for cisplatin in SCLC chemotherapy regimens in an effort to decrease non-hematologic toxicities. Randomized trials comparing cisplatin and carboplatin suggest that these compounds may have similar efficacy. One such study was conducted by the Hellenic Cooperative Oncology Group, which randomized 147 patients with either limited or extensive disease to receive etoposide 100 mg/m2 on Days 1 to 3 and cisplatin 100 mg/m2 or carboplatin 300 mg/m2 on Day 1 of each cycle [64]. Concurrent radiation was also administered to responding patients starting with the third cycle. Response and survival were similar in the 2 arms. Nausea, vomiting, nephrotoxicity, and neurotoxicity were significantly lower in the patients who received carboplatin, as was Grade 4 leukopenia. Unfortunately, the sample size was inadequate to confirm equivalent efficacy. A subsequent meta-analysis evaluated individual subject data from 4 randomized trials with a total of 663 patients and found that median OS, median PFS, and response rates were similar in the cisplatin and carboplatin arms. While hematologic toxicities were higher in patients treated with carboplatin, non-hematologic toxicities were increased in patients treated with cisplatin [65]. Based on these data, etoposide/carboplatin can be considered an appropriate 1L regimen to treat SCLC, particularly in patients who cannot tolerate cisplatin.

Multiple randomized studies have evaluated whether continuation beyond 4 to 6 cycles of chemotherapy is necessary. Overall survival is not improved if patients receive additional cycles of the same regimen used for induction [66] [67], maintenance oral etoposide or sunitinib after an etoposide-containing 1L regimen [68] [60] [69], or consolidation with different chemotherapeutic regimens after 4 cycles of EP [70] [71]. Treatment beyond 6 cycles of chemotherapy is not recommended for ES-SCLC by the National Comprehensive Cancer Network [72], the European Society of Medical Oncology Guidelines [73], or the American Society of Clinical Oncology [74]. Recent trials in this patient population have administered 4 cycles of therapy [60] [61] [63].

4.1.2.2 Prophylactic Cranial Irradiation

Brain metastases are common in SCLC. Approximately 18% of patients have central nervous system involvement at diagnosis [75], and another 20% to 25% of patients develop brain metastasis during the course of their disease, the likelihood increasing with lengthening

survival [76] [77]. At postmortem examination, brain metastases are found in up to 65% of patients who had SCLC [78].

In a meta-analysis of almost 1,000 patients in 7 trials between 1977 and 1995, patients were evaluated with and without PCI after initially obtaining a complete response [79]. Prophylactic cranial irradiation doses ranged from 24 to 40 Gy in most patients. Three-year survival rates increased from 15% without PCI to almost 21% with PCI. Additional findings included a significantly decreased probability of brain metastases and increased likelihood of disease-free survival. Higher doses of radiation appeared to be more effective in preventing brain metastases, but had no impact on survival. A trend toward a decreased risk of brain metastases was observed when PCI was administered earlier.

A survival benefit with PCI in patients with ES-SCLC who had a response to chemotherapy was demonstrated in an EORTC randomized trial (N=286) [80]. Significantly, addition of PCI therapy improved the rate of 1-year freedom from symptomatic brain metastases from 14.6% to 40.4% and improved the 1-year survival rate from 13.3% to 27.1%. Various fractionation schemes were used; the most common were 20 Gy in 5 fractions and 30 Gy in 10 fractions. The trial did not mandate pre-treatment brain imaging to rule out clinically occult brain metastases, which has raised the question of whether the observed survival benefit was due to treatment of patients who already had detectable brain metastases. Regardless, the results of the EORTC trial established PCI as a standard consideration for all patients with ES-SCLC who achieve a response to initial therapy. Yet, the American Society of Clinical Oncology Guidelines note that this may be subject to change upon final publication of a recently conducted study in Japan. The study randomized 163 patients with ES-SCLC who responded to 1L therapy to either PCI (25 Gy in 10 fractions) or observation and failed to demonstrate a survival advantage for PCI [74].

More recently, standard-dose versus higher-dose PCI has been evaluated after complete response (CR) in patients with limited stage small cell lung cancer (LS-SCLC) in an Intergroup trial [81]. Seven hundred twenty patients were randomized to either 25 Gy in 10 fractions or 36 Gy delivered in 18 daily fractions of 2 Gy or 24 twice-daily fractions of 1.5 Gy. There was no significant difference in incidence of brain metastases between the standard-dose group and the high-dose group. The OS was significantly worse in the higher-dose group, further establishing 25 Gy in 10 fractions as the standard dose of PCI for patients with LS-SCLC.

Prophylactic cranial irradiation is associated with AEs such as fatigue, hair loss, and decreased quality of life [73]. Long-term survivors have neurologic and intellectual impairment, as well as abnormalities on computed tomography (CT) imaging that may be related to PCI [82] [83], which for some, causes reluctance to propose this treatment. Consequently, PCI guidelines recommend that patients who proceed with PCI have a good performance status and adequate neurocognitive functioning, and that a full discussion occurs between the patient and physician, especially in extensive stage disease [73] [72].

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

Small cell lung cancer remains a worldwide public health problem; it is a major cause of cancer mortality and is strongly associated with tobacco exposure [84] [85]. While in the United States there has been a decline in prevalence of tobacco use resulting in a gradual decrease in SCLC incidence over the past decades, SCLC still accounts for 14% of all lung cancers, with approximately 30,000 patients diagnosed annually [86] [87]. Approximately 275,000 patients worldwide are diagnosed with SCLC annually [84] [85].

Small cell lung cancer is an aggressive neuroendocrine malignancy with a unique natural history characterized by a short doubling time, high growth fraction, and early development of widespread metastases. Although a chemotherapy- and radiation-sensitive disease, SCLC typically recurs rapidly after primary treatment, with only 6% of patients surviving 5 years from diagnosis.

Treatment of SCLC is notable for the lack of major developments; nearly 4 decades after the introduction of an EP doublet, therapeutic options have remained virtually unchanged, with correspondingly little improvement in survival rates.

Radiation therapy is administered to patients with LS-SCLC, whose cancer is confined to the chest in a single tolerable radiation field. Patients with LS-SCLC or ES-SCLC who achieve a response to 1L platinum-based therapy generally are offered PCI, which has been shown to decrease the risk of intracranial recurrence and improve OS [79] [80]. Additional efforts at improving outcomes with 1L therapy for SCLC patients have been unsuccessful. Examples include the use of irinotecan instead of etoposide (in Western countries), alternating multi-drug combinations, addition of a third chemotherapeutic drug to etoposide and cisplatin, and prolonging the number of cycles of etoposide and cisplatin or carboplatin [88].

First-line treatment for SCLC yields optimal tumor response rates as high as 60% to 80%, which unfortunately translates to cure in only approximately 20% of patients with LS-SCLC [89]. Essentially all patients with ES-SCLC, and the majority of patients with LS-SCLC, suffer relapse within months of completing initial therapy. The strongest predictor of outcome for patients with relapsed SCLC is the duration of remission. Patients with sensitive disease, who maintain a response to initial treatment for 3 months or more, have a response rate to additional chemotherapy of about 25% and a median survival of about 6 months from the time of relapse. In contrast, those patients with refractory disease who either have no response to initial therapy or progress within 3 months, rarely benefit from additional treatment, with response rates <10% and median survival of 4 months.

Topotecan is the only Food and Drug Administration (FDA)-approved agent for recurrent or progressive SCLC, based on the results of three Phase 3 trials [90] [91] [92]. There are no accepted regimens for patients whose disease has progressed after 1L and 2L treatments for SCLC. This is in stark contrast to the progress that has been made in the treatment of NSCLC, thus underscoring the critical need for more effective therapies in SCLC.

When considering new approaches to 1L treatment of SCLC, the dramatic initial tumor response to an EP regimen seen in the large majority of SCLC patients must be acknowledged; however, in nearly all cases, the tumors become resistant to this treatment.

Several lines of evidence support modulation of immune response in SCLC as a treatment modality. The disease is associated with immunogenic effects, evidenced by the prolonged survival of patients with autoantibodies (ie, anti-Hu) and neurologic paraneoplastic syndromes [93]. The expression of major histocompatibility complex antigens is reduced in SCLC and this may play a role in this tumor's ability to escape immune surveillance [94] [95]. Interestingly, effector T-cells associated with cytolytic responses are significantly higher in the peripheral blood of patients with LS-SCLC compared to those with ES-SCLC and in long term disease-free survivors relative to those with recurrent disease [96]. More recently, the PD-1/PD-L1 pathway, a major target of anti-tumor immunotherapy, has been interrogated in SCLC utilizing immunohistochemistry (IHC) and RNA-expression to evaluate the presence of PD-L1 in primary and metastatic tumor tissue as well as in TILs [97] [98] [99] [100] [101]. In general, 50% to 80% of tumor specimens were PD-L1-positive (ie, >5% of cells in the specimen expressed PD-L1). In several of these reports, when other patient characteristics and treatment outcomes were considered, patients with PD-L1-positive tumors had a longer OS, and higher PD-L1 expression strongly correlated with limited-stage disease [98] [99] [100] [101]. However, each of these studies utilized different types of specimens, as well as antibodies.

Mutational burden appears to be an important determinant of response to immune checkpoint inhibitors. In a recent study analyzing tumor mutational burden in NSCLC patients treated with pembrolizumab, higher mutational burden was associated with improved objective response, durable clinical benefit, and prolonged PFS [102]. The association between response to PD-1 inhibitors, mutational burden, and tobacco exposure may have important implications for SCLC, as this disease is strongly associated with smoking and has a markedly elevated mutation burden, as highlighted previously.

KEYNOTE-028 is a Phase 1b multi-cohort study of pembrolizumab for the treatment of PD-L1-positive, advanced solid tumors including SCLC. Of the 147 subjects with evaluable ES-SCLC biopsy specimens who were screened, 42 (29%) had PD-L1-positive tumors and, of these, 24 previously treated subjects were eventually enrolled. Notably, 21 patients (87.5%) were in need of third-line or greater therapy. The patients were treated with pembrolizumab monotherapy for up to 2 years. Median duration of follow-up was 9.8 months (range: 0.5 to 24.0). The ORR was 37.5% (95% confidence interval [CI] 18.8 to 59.4) and included 1 CR and 8 PRs. Median DOR was 9.0 months (range: 1.9 to 19.9+). Median PFS was 1.9 months (range: 1.7 to 5.9) and at 6 and 12 months, 29.8% and 24.8% of subjects were alive and progression-free, respectively. Median OS was 9.7 months (95% CI 4.1 to not reached); 66.0% and 35.7% of subjects were alive at 6 and 12 months, respectively. Treatment-related AEs were reported for 66.0% of subjects, including 2 subjects with Grades 3 to 5 treatment-related AEs. No new safety concerns were identified [103]. These results demonstrate that pembrolizumab monotherapy has meaningful anti-tumor activity in heavily pre-treated subjects with PD-L1-positive SCLC. In contrast, studies of topotecan as 2L treatment of SCLC demonstrated response rates of approximately 18%,

median survival of 6 months, and duration of response of 7.5 months [104] [105] [106] [107]. Based on this information, incorporating pembrolizumab treatment in the 1L setting in SCLC patients may lead to further improvement in outcomes.

Recently, Langer and colleagues reported results from KEYNOTE-021 Cohort G, a Phase 2 randomized trial comparing pembrolizumab/pemetrexed/carboplatin with pemetrexed/carboplatin alone for the treatment of subjects with newly diagnosed NSCLC regardless of PD-L1 tumor expression [108]. The ORR was 55% in the pembrolizumab/pemetrexed/carboplatin arm compared with 29% in the pemetrexed/ carboplatin alone arm (p=0.0016), and responses occurred 1 month earlier in the pembrolizumab/pemetrexed/carboplatin arm. The improvement in response was observed in subjects with tumors of all PD-L1 expression levels. Progression-free survival was improved for the pembrolizumab/pemetrexed/carboplatin arm compared with the pemetrexed/ carboplatin alone arm (13 months versus 8.9 months, respectively; p=0.0102). These data indicate that pembrolizumab with chemotherapy has the potential to be an effective 1L treatment for SCLC and potentially may be a regimen that can change outcomes in this disease.

Based on the previously mentioned data and a critical need for new therapies in SCLC, we are undertaking this worldwide, randomized, placebo-controlled, Phase 3, parallel group, multi-site, double-blind trial of pembrolizumab plus SOC chemotherapy (EP) in subjects with ES-SCLC who have not previously received systemic therapy.

4.2.2 Rationale for Dose Selection/Regimen/Modification

4.2.2.1 Rationale for the Dose of Pembrolizumab

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

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

Among the 8 randomized dose-comparison studies, a total of 2262 subjects with melanoma or NSCLC were enrolled, covering different disease settings (treatment naïve, previously treated, PD-L1 enriched, and all-comers) and different treatment settings (monotherapy and in combination with chemotherapy). Five studies compared 2 mg/kg Q3W and 10 mg/kg Q3W (KEYNOTE-001 B2, KEYNOTE-001 D, KEYNOTE-002, KEYNOTE-010, and

KEYNOTE-021), and 3 studies compared 10 mg/kg Q3W and 10 mg/kg Q2W (KEYNOTE-001 B3, KEYNOTE-001 F2, and KEYNOTE-006). All of these studies demonstrated flat dose- and exposure-response relationships across the doses studied representing an approximate 5- to 7.5-fold difference in exposure. The 2 mg/kg (or 200 mg fixed-dose) Q3W provided similar responses to the highest doses studied. Subsequently, flat dose-exposure-response relationships were also observed in subjects with other tumor types, including head and neck cancer, bladder cancer, gastric cancer, and classical Hodgkin Lymphoma, confirming 200 mg Q3W as the appropriate dose independent of the tumor type. These findings are consistent with the mechanism of action of pembrolizumab, which acts by interaction with immune cells, and not via direct binding to cancer cells.

Additionally, pharmacology data clearly show target saturation at 200 mg Q3W. First, PK data in KEYNOTE-001 evaluating 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 demonstrated that pembrolizumab 200 mg Q3W achieves full PD-1 saturation in both blood and tumor.

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

4.2.2.2 Rationale for Use of Comparator/Placebo

The use of saline placebo in combination with standard chemotherapy will ensure the objectivity of investigator-assessed progression, as well as any decisions to interrupt/discontinue therapy.

4.2.3 Rationale for Efficacy Endpoints

4.2.3.1 Primary Efficacy Endpoints

Primary: This trial has dual primary endpoints of PFS and OS.

PFS is an acceptable measure of clinical benefit for a randomized Phase 3 trial that demonstrates superiority of a new antineoplastic therapy, especially if the magnitude of effect is large and the therapy has an acceptable risk-benefit profile. PFS, as assessed by BICR per RECIST 1.1 (modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ), will be used to determine the dates of progression as this methodology is accepted by regulatory authorities. Images read by BICR blinded to treatment assignment can minimize bias in the response assessments. In addition, final determination of radiologic PD will be based on the BICR assessment of progression, rather than local site investigator/radiology assessment. Expedited assessment by the BICR in

instances of suspected radiologic progression identified at the site (verification of PD) will be communicated to the site study team.

Notably, PFS has demonstrated strong potential surrogacy for OS in 1L treatment of ES-SCLC and may be a good alternative endpoint to OS in this disease [109].

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

4.2.3.2 Secondary Efficacy Endpoints

The key secondary efficacy endpoint of this study is ORR assessed by BICR using RECIST 1.1 modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ. Additionally, DOR assessed by BICR according to RECIST 1.1 modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ is a secondary endpoint.

4.2.3.3 Safety Endpoints

The incidence of AE/SAEs (including fatal SAEs), immune-related AEs, laboratory abnormalities, and rates of dose interruption and discontinuation due to AEs are important endpoints for safety and tolerability evaluations.

4.2.3.4 Patient Reported Outcomes

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

EORTC QLQ-C30 was developed to assess the quality of life of subjects with cancer. It has been translated into 81 languages, validated, and used in more than 3000 studies worldwide. It contains 5 functioning scales (physical, role, cognitive, emotional, and social), 3 symptom scales (fatigue, nausea, and 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 (ie, coughing, hemoptysis, dyspnea, and pain) and side effects from chemotherapy and radiation (ie, hair loss, neuropathy, sore mouth, and 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 into 64 languages and validated.

The EQ-5D-5L is a standardized instrument for use as a measure of health outcome. The EQ-5D-5L will provide data for use in economic models and analyses including developing

health utilities or quality-adjusted life-years. The 5 health state dimensions addressed in this instrument are mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems.

4.2.3.5 Immune-related RECIST

Immune-related RECIST is RECIST 1.1 adapted to account for the unique tumor response seen with immunotherapeutics as described by Nishino et al [110]. The assessment of unidimensional target lesions and response categories per irRECIST are identical to RECIST 1.1. However, Merck has implemented an adaptation related to new lesions, non-target lesions, and tumor burden assessment in order to confirm radiographic progression.

Immunotherapeutic agents such as pembrolizumab may produce anti-tumor effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents, and can manifest a clinical response after an initial increase in tumor burden or even the appearance of new lesions. Thus, standard RECIST 1.1 may not provide an accurate response assessment for immunotherapeutic agents such as pembrolizumab. Based on an analysis of patients with melanoma enrolled in KEYNOTE-001 [111], 7% of evaluable patients experienced delayed or early tumor pseudo-progression. Of note, patients who had progressive disease by RECIST 1.1 but not by irRECIST, had longer OS than patients with PD by both criteria. Additionally, the data suggest that RECIST 1.1 may underestimate the benefit of pembrolizumab in approximately 15% of patients. These findings support the need to apply a modification to RECIST 1.1 that takes into account the unique patterns of atypical response to immunotherapy and enable treatment beyond initial radiographic progression.

Local site investigators will use irRECIST to assess tumor response and progression and to make treatment decisions.

For further information on irRECIST, see Section 7.1.2.7.6.

4.2.3.6 Planned Exploratory Biomarker Research

Cancer immunotherapies represent an important and novel class of anti-tumor agents. However, the mechanism of action of these exciting new therapies is not completely understood and much remains to be learned regarding how best to leverage these new drugs in treating subjects. Thus, to aid future subjects, it is important to investigate the determinants of response or resistance to cancer immunotherapy as well as determinants of AEs in the course of our clinical trials. These efforts will identify novel predictive/pharmacodynamic biomarkers and generate information that will better guide

single-agent and combination therapy with immuno-oncology drugs. To identify novel biomarkers, we will collect biospecimens (eg, blood components, tumor material) to support analyses of cellular components (eg, protein, DNA, RNA, metabolites) and other circulating molecules. Investigations may include but are not limited to:

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

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

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

Proteomics and IHC using blood and tumor: Tumor and blood samples from this study may undergo proteomic analyses (eg, PD-L1 IHC). PD-L1 protein level in tumor sections, assessed by IHC, has been shown to correlate with response to pembrolizumab in subjects with NSCLC, and an in vitro diagnostic device has been developed for use with pembrolizumab in NSCLC. Preliminary data indicate that this association may also be true in additional cancer types (ie, triple-negative breast cancer, head and neck cancer, and gastric cancer). Since many tumor or blood-derived proteins may correlate with response to pembrolizumab, tumor tissue may be subjected to proteomic analyses using a variety of platforms including, but not limited to, immunoassays and liquid chromatography/mass

spectrometry. This approach could identify novel protein biomarkers to aid in patient selection for pembrolizumab therapy.

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

4.2.3.7 Future Biomedical Research

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

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

4.3 Benefit/Risk

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

As described in Section 4.2.1, KEYNOTE-028 demonstrated that pembrolizumab monotherapy has meaningful anti-tumor activity in heavily pre-treated subjects with PD-L1-positive SCLC. Pembrolizumab in combination with chemotherapy has significant clinical activity as 1L therapy in subjects with advanced NSCLC, regardless of PD-L1 expression, as shown in KEYNOTE-021 Cohort G (Section 4.2.1). Considering the high unmet medical need for new and tolerable treatment options in subjects with newly diagnosed ES-SCLC, the anti-tumor activity and the favorable safety profile of pembrolizumab in combination with chemotherapy regimens for other solid tumors, a combination of PD-1 blockade plus chemotherapy is a promising therapeutic strategy and the benefit-risk assessment for subjects included in this trial is considered to be favorable.

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

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

Male and female subjects with ES-SCLC 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 documented new diagnosis of SCLC by histology or cytology from brushing, washing, or needle aspiration of a defined lesion. Subjects who do not have histology samples (defined as core or excisional biopsy, or resections) will need to undergo a new biopsy to provide a tissue sample.

2. Have extensive stage disease defined as Stage IV (T any, N any, M 1a/b) by the American Joint Committee on Cancer, Seventh Edition.

3. Have at least 1 lesion that meets the criteria for being measurable, as defined by RECIST 1.1, and is appropriate for selection as a target lesion, as determined by local site investigator/radiology review. Lesions that appear measurable, but have undergone palliative irradiation, cannot be target lesions.

4. Have provided archival tumor tissue sample or newly obtained core or excisional biopsy of a tumor lesion not previously irradiated. Formalin-fixed, paraffin-embedded tissue blocks are preferred to slides.

5. Have ECOG Performance Status of 0 or 1. See Section 12.3 for definitions.

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

7. Have adequate organ function as indicated by the following laboratory values (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	≥8 g/d [a]
Renal	
Serum creatinine OR calculated creatinine clearance (CrCl)[b] (GFR can also be used in place of creatinine or CrCl)	≤1.5 × ULN **OR** ≥60 mL/min for subjects with creatinine levels >1.5× ULN receiving cisplatin ≥50 mL/min for subjects with creatinine levels >1.5 × ULN receiving carboplatin
Hepatic	
Serum total bilirubin	≤1.5 × ULN OR Direct bilirubin ≤ULN for subjects with total bilirubin levels >1.5 × ULN
AST (SGOT) and ALT (SGPT)	≤2.5 × ULN ≤5 × ULN for subjects with liver metastases
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT)	≤1.5 × ULN unless the subject is receiving anticoagulant therapy as long as PT or INR is within therapeutic range of intended use of anticoagulants

Abbreviations: ALT (SGPT)=alanine aminotransferase (serum glutamic pyruvic transaminase); AST (SGOT)=aspartate aminotransferase (serum glutamic oxaloacetic transaminase); GFR=glomerular filtration rate; INR=International Normalized Ratio; ULN=upper limit of normal.
[a] Criterion must be met without erythropoietin dependency and without packed red blood cell (pRBC) transfusion within last 2 weeks.
[b] Creatinine clearance (CrCl) should be calculated per institutional standard.
Note: This table includes eligibility-defining laboratory value requirements for treatment; laboratory value requirements should be adapted according to local regulations and guidelines for the administration of specific chemotherapies.

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

9. If female subject of childbearing potential, have a negative urine or serum pregnancy test within 72 hours prior to receiving the first dose of study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

10. If female and of childbearing potential, be willing to use an adequate method of contraception as outlined in Section 5.7.2, starting with the first dose of study medication through 120 days after the last dose of pembrolizumab or saline placebo or up to 180 days after last dose of chemotherapeutic agents, whichever is later.

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

11. If male and of childbearing potential, agree to use an adequate method of contraception as outlined in Section 5.7.2, starting with the first dose of study medication through 120 days after the last dose of pembrolizumab or saline placebo or up to 180 days after last dose of chemotherapeutic agents, whichever is later.

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

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

5.1.3 Subject Exclusion Criteria

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

1. Has received prior systemic therapy for the treatment of SCLC.

   Note: Palliative radiation therapy is allowed until 7 days prior to the first dose of trial medication, provided that the radiated lesion is clinically stable and the patient is not receiving steroids for at least 7 days prior to the first dose of study medication. The radiated lesion must not be a thoracic lesion and must not be included as a target lesion for RECIST 1.1 measurements.

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

   Note: Subjects who have entered the follow-up phase of an investigational trial may participate as long as it has been at least 4 weeks since the last dose of the previous investigational agent.

3. Is expected to require any other form of antineoplastic therapy for SCLC, including radiation therapy, while on study.

   Note: Patients with PR or CR will be offered PCI therapy at the completion of the 4 cycles of chemotherapy with or without pembrolizumab.

4. Has known central nervous system (ie, brain and/or spinal cord) metastases and/or carcinomatous meningitis. Subjects with brain metastases may participate only if they satisfy all of the following:

   - Completed treatment (eg, whole brain radiation treatment [WBRT], stereotactic radiosurgery, or equivalent) at least 14 days prior to the first dose of trial treatment,

- Have no evidence of new or enlarging brain metastases confirmed by post-treatment repeat brain imaging (using the same modality) performed at least 3 weeks after pre-treatment brain imaging, and

- Are neurologically stable without the need for steroids for at least 7 days before first dose of trial treatment as per local site assessment.

5. Has had major surgery within 3 weeks prior to receiving the first dose of trial treatment or has not recovered adequately from toxicity and/or complications from an intervention prior to receiving the first dose of study treatment.

6. Has a history of non-infectious pneumonitis that required steroids or has current pneumonitis.

7. Has a known history of interstitial lung disease.

8. Has a known additional malignancy that is progressing or requires active treatment. Exceptions include early stage cancers (carcinoma in situ or Stage 1) treated with curative intent, basal cell carcinoma of the skin, squamous cell carcinoma of the skin, in situ cervical cancer, or in situ breast cancer that has undergone potentially curative therapy.

9. Has active autoimmune disease that has required systemic treatment in the past 2 years (ie, with use of disease-modifying agents, corticosteroids, or immunosuppressive drugs). Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment.

10. Has a known history of, or active, neurologic paraneoplastic syndrome.

11. Has clinically active diverticulitis, intra-abdominal abscess, gastrointestinal obstruction, and/or abdominal carcinomatosis.

12. Has a history of a severe hypersensitivity reaction to treatment with another monoclonal antibody.

13. Is taking chronic systemic steroids (in doses exceeding 10 mg daily of prednisone equivalent) within 7 days prior to the first dose of trial treatment.

    Note: Subjects with asthma or chronic obstructive pulmonary disease that require intermittent use of bronchodilators, inhaled steroids, or local steroid injections would not be excluded from the study.

14. Has a diagnosis of immunodeficiency or is receiving any form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment.

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

16. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent or with an agent directed to another co-inhibitory T-cell receptor (ie, CTLA-4, OX-40, CD137) or has previously participated in a Merck pembrolizumab (MK-3475) clinical trial.

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

18. Has an active infection requiring systemic therapy.

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

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

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

21. Has a known history of active TB (Bacillus Tuberculosis).

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

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

24. Has symptomatic ascites or pleural effusion. A subject who is clinically stable following treatment for these conditions (including therapeutic thoraco- or paracentesis) is eligible.

25. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the study starting with the screening visit through 120 days after the last dose of pembrolizumab or saline placebo or up to 180 days after last dose of chemotherapeutic agents, whichever is later.

5.2 Trial Treatment(s)

The treatments to be used in this trial are outlined below in Table 2.

Table 2 Trial Treatments

Drug or Biologic	Dose/ Potency	Dose Frequency	Route of Administration	Regimen/ Treatment Period	Use
Pembrolizumab	200 mg	Q3W	IV infusion	Day 1 of each cycle prior to chemotherapy	Experimental
Saline	Not applicable	Q3W	IV infusion	Day 1 of each cycle prior to chemotherapy	Placebo comparator
Carboplatin	AUC 5	Q3W	IV infusion	Day 1 of each cycle	Standard of care
Cisplatin	75 mg/m^2	Q3W	IV infusion	Day 1 of each cycle	
Etoposide	100 mg/m^2	Q3W	IV infusion	Days 1, 2, 3 of each cycle	

Trial treatment should begin on the day of randomization or as soon as possible, but no later than 3 days after randomization.

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

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

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

5.2.1 Dose Selection/Modification

5.2.1.1 Dose Selection (Preparation)

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

Standard chemotherapeutic agents (etoposide and carboplatin or cisplatin) will be prepared and administered as per the local approved product label. Appropriate infusion times for each agent are noted in the respective subsections of Section 5.2.2.2.

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

5.2.1.2 Dose Modification

If a subject experiences a >10% weight change during Cycles 1 to 4, the doses of etoposide and cisplatin/carboplatin should be recalculated.

Dose modifications due to AEs will depend on the investigator's assessment of causality. If appropriate, the investigator may attribute each toxicity event to etoposide, cisplatin/carboplatin, or pembrolizumab alone or to the combination and use a stepwise dose reduction according to Table 3 through Table 7. Dose modifications must be based on the maximum toxicity experienced during a cycle. Toxicity must resolve to Grade ≤1 or baseline prior to resuming the subsequent cycle, with the exception of alopecia, Grade 2 fatigue, endocrine-related AEs requiring treatment or hormone replacement, which may be Grade ≤2, and creatinine clearance, for which the guidelines in Section 5.2.1.2.2 may be followed.

If a dose reduction for toxicity occurs with any agent, the dose may not be re-escalated. Subjects can have a maximum of 2 dose modifications (if applicable) to each of the components of study therapy throughout the course of the study for toxicities. If a subject experiences several toxicities and there are conflicting recommendations, the most conservative dose adjustment recommended should be followed (ie, dose reduction appropriate to the most severe toxicity). Subjects who require a third dose modification to any particular component will have that agent discontinued. In the absence of the agent thought to be causing toxicity, treatment can continue with pembrolizumab or saline placebo and the remaining chemotherapeutic drug.

Reduction of 1 chemotherapy agent and not the other agent is appropriate if, in the opinion of the investigator, the toxicity is clearly related to one of the treatments. If, in the opinion of the investigator, the toxicity is related to the combination of both chemotherapy agents, both drugs should be reduced according to recommended dose modifications. If the toxicity is related to the combination of 3 agents, all 3 agents should be reduced (if applicable), interrupted, or discontinued according to the recommended dose modifications.

Pembrolizumab dose reductions are not permitted. Pembrolizumab treatment may be delayed/interrupted for a maximum of 12 weeks or discontinued due to toxicity.

Subjects may have chemotherapy discontinued and continue on pembrolizumab or saline placebo alone. Similarly, subjects may discontinue pembrolizumab or saline placebo and continue on chemotherapy alone during the first 4 cycles, if appropriate. Any requests for unblinding will be considered on an individual subject basis and only after consultation with the Sponsor.

During Cycles 1 through 4 of pembrolizumab + EP or placebo + EP:

- If etoposide dosing is delayed or interrupted, the platinum agent and pembrolizumab or saline placebo should also be delayed/interrupted. If EP is delayed or interrupted during Cycles 1 through 4, patients should be seen weekly until toxicity resolves.

- If cisplatin/carboplatin dosing is delayed or interrupted, etoposide and pembrolizumab or saline placebo should also be delayed/interrupted. If EP is delayed or interrupted during Cycles 1 through 4, patients should be seen weekly until toxicity resolves.

- If pembrolizumab or saline placebo dosing is delayed or interrupted, EP therapy can continue as scheduled. Pembrolizumab or saline placebo administration should be attempted at the next cycle of therapy.

- Each chemotherapy cycle may not be delayed by more than 3 weeks (>21 consecutive days) despite supportive treatment. If only one of the agents is thought to be causing the specified toxicity leading to a 21-day delay of administration of the next cycle, that chemotherapeutic agent can be stopped and treatment can continue with pembrolizumab or saline placebo and the remaining chemotherapy drug. Pembrolizumab/placebo dosing can continue with 1 agent or as monotherapy.

The NCI CTCAE 4.0 must be used to grade the severity of AEs. All dose modifications should be based on the AE requiring the greatest dose modification. Dose modifications are detailed in Table 3 through Table 7.

Table 3 Dose Modifications for Study Drugs

	Etoposide	**Cisplatin**	**Carboplatin**	**Pembrolizumab/ Placebo**
Dose Level 0 (starting dose)	100mg/m^2/day	75mg/m^2	AUC 5	200 mg fixed dose
Dose Level -1	75mg/m^2/day	56mg/m^2	AUC 4	Dose reduction not permitted
Dose Level -2	50mg/m^2/day	38mg/m^2	AUC 3	Dose reduction not permitted
Dose Level -3	Discontinue	Discontinue	Discontinue	Dose reduction not permitted

5.2.1.2.1 Pembrolizumab

Adverse events (both non-serious and serious) associated with pembrolizumab exposure may have an immunologic etiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is

critical to reduce complications. Based on existing clinical trial data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids, and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, or skin biopsy may be included as part of the evaluation. Based on the severity of the irAE, withhold or permanently discontinue pembrolizumab and administer corticosteroids. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab are provided in Table 4.

Table 4 Dose Modification and Toxicity Management Guidelines for Immune-Related 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		
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 returns to baseline or is stable

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
	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	New 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 thioamides 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		
Myocarditis	Grade 1 or 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		

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

Abbreviations: AE=adverse event, ALT=alanine transaminase, AST=aspartate transaminase, CTCAEv4.0=Common Terminology Criteria for Adverse Events version 4.0, irAE=immune-related adverse event, IV=intravenous, T1DM=Type 1 diabetes mellitus

1. Withholding or permanently discontinuing pembrolizumab is at the discretion of the investigator or treating physician.
2. For subjects with Grade 3 or 4 immune-related endocrinopathy where withholding of pembrolizumab is required, pembrolizumab may be resumed when AE resolves to Grade ≤2 and is controlled with hormonal replacement therapy or achieved metabolic control (in case of T1DM).

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

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

Table 5 Pembrolizumab Infusion Reaction Dose Modification and Treatment Guidelines

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

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

Other allowed dose interruptions for pembrolizumab

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

5.2.1.2.2 Chemotherapeutic agents (etoposide/platinum)

Study drug-related toxicities must be resolved to baseline or Grade ≤1 (with the exception of alopecia, Grade 2 fatigue, and endocrine-related AEs requiring treatment or hormone replacement, which may be Grade ≤2, and creatinine clearance, for which the guidelines provided below may be followed) prior to administering the next dose. Subjects must not receive the next cycle of chemotherapy if any of the following apply:

- Absolute neutrophil count (ANC) <1,500/mm^3
- Platelet count <100,000/mm^3
- Hemoglobin level <8 g/dL
- Total bilirubin level >1.5 × ULN
- Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels ≥2.5 × ULN, or ≥5 × ULN if liver metastases are present

Recommended dose modifications for key chemotherapy toxicities (etoposide and cisplatin/carboplatin) are outlined in Table 6 and Table 7. These serve as a guide and do not replace investigator judgment and applicable local label recommendations, if more stringent. A subject is allowed to switch from cisplatin to carboplatin if the subject develops unexpected toxicities with the use of cisplatin (including hearing loss), becomes ineligible for further cisplatin therapy, and/or the investigator considers switching to carboplatin to be in the best interest of the subject.

A maximum of 2 dose reductions per chemotherapy agent are permitted; if additional reductions are required, that particular agent must be discontinued. Once the dose has been decreased, it should remain reduced for all subsequent administrations or be further reduced, if necessary. There will be no dose escalations in this study. Each chemotherapy cycle may not be delayed by more than 3 weeks (>21 consecutive days) despite supportive treatment. If unacceptable toxicities related to etoposide, cisplatin, or carboplatin occur, and only one of the agents is thought to be causing a specified toxicity leading to a 21-day delay of administration of the next cycle, as determined by investigator judgment, the agent will be discontinued but the other drugs may be continued.

Table 6 Recommended Chemotherapy Dose Modifications for Hematological Toxicity

Drug Related Toxicity[a]	Etoposide	Cisplatin	Carboplatin
	Dose Level (DL) from Table 3		
Neutrophils (ANC) <500/mm^3 without fever	DL -1	DL -1	DL -1
Febrile neutropenia (fever ≥38.5°C and ANC <1,000/mm^3)	DL -1	DL -1	DL -1
Platelets <50,000/mm^3 without significant bleeding or requiring blood transfusion	DL -1	DL -1	DL -1
Platelets <50,000/mm^3 with Grade ≥2 hemorrhage or requiring blood transfusion	DL -2	DL -2	DL -2
Grade 4 hemoglobin	DL -1	DL -1	DL -1

Abbreviations: ANC=absolute neutrophil count, DL=dose level

Note: If toxicity can clearly be attributed to one of the drugs, the investigator may choose to only reduce the dose of one of the chemotherapy agents. Investigators may decide to use supportive measures/treatment and/or secondary prophylaxis as per institutional standards (eg, filgrastim, pegfilgrastim, transfusions) instead of dose reductions for the next cycle, if considered in the best interest of the subject.

[a] Should the hematologic toxicity recur, the dose of the agent could be reduced further. However, not more than 2 dose reductions per chemotherapy agent are permitted.

Table 7 Recommended Chemotherapy Dose Modifications for Non-hematologic Toxicity

Drug Related Toxicity[a]	**CTCAE Grade**	**Etoposide**	**Cisplatin**	**Carboplatin**
		Dose Level (DL) from Table 3		
Nausea/vomiting	Grade ≥3[b]	DL 0	DL -1	DL -1
Mucositis	Grade ≥3[b]	DL -1	DL -1	DL -1
Diarrhea	Grade ≥3[b]	DL -1	DL -1	DL -1
Peripheral neuropathy	Grade 2	No modification	DL -1[c]	No modification
	Grade 3	No modification	Discontinue[d]	DL -1
	Grade 4	No modification	Discontinue	DL -1
Total bilirubin	Grade 2	DL -2	No modification	No modification
	Grade 3	Discontinue	No modification	No modification
	Grade 4	Discontinue	No modification	No modification
AST or ALT Elevation	Grade 3	DL -1	DL -1	DL -1
	Grade 4	Discontinue	Discontinue	Discontinue
Other Non-hematologic Toxicity (except fatigue and transient arthralgia and myalgia)	Grade ≥3	DL -1	DL -1	DL -1

Note: If considered in the best interest of the subject, and consistent with local practice, investigators may decide to use supportive measures/treatment, and/or secondary prophylaxis instead of dose reductions for the next cycle. Also, if toxicity can clearly be attributed to one of the drugs, the investigator may choose to only reduce the dose of one of the chemotherapy agents.

[a] Should the toxicity recur, the dose of the agent could be reduced further. However, not more than 2 dose reductions per chemotherapy agent are permitted.

[b] The first occurrence of Grade ≥3 nausea/vomiting, mucositis, and diarrhea should be managed symptomatically with optimal medical therapy, and improve to Grade ≤1 prior to proceeding with additional therapy. Should these events recur despite aggressive management, a dose modification can be employed once the AE improves to Grade ≤1.

[c] If Grade 2 neurotoxicity recurs after DL -1, drug will be given at DL -2 or switch can be made to the appropriate dose of carboplatin at the discretion of the investigator in consultation with the Sponsor. If Grade 2 neurotoxicity persists after 2 dose level reductions and 21-day hold, switch can be made to the appropriate dose of carboplatin at the discretion of the investigator in consultation with the Sponsor.

[d] If Grade 3 neurotoxicity occurs, cisplatin will be discontinued and, upon improvement, a switch can be made to the appropriate dose of carboplatin at the discretion of the investigator in consultation with the Sponsor.

Creatinine clearance:

Creatinine clearance (CrCl) will be based on either the Cockcroft-Gault formula (Section 5.2.2.2.1) or another acceptable standard formula.

For patients receiving cisplatin, the scheduled dose of cisplatin may only be administered if the calculated CrCl is ≥50 mL/min:

- If CrCl falls to <50 mL/min, delay the start of that cycle for ≤21 days. In the interim, monitor renal function weekly and consider intravenous (IV) hydration. When CrCl improves to ≥50 mL/min, decrease cisplatin to dose level (DL) -1 (Table 3). Alternatively, if in the investigator's judgment it is in the best interest of the patient, cisplatin can be switched to carboplatin if the calculated CrCl is appropriate, and in consultation with the Sponsor.

- At the second occurrence of CrCl <50 mL/min, decrease cisplatin to DL -2 upon improvement of CrCl to ≥50 mL/min. Alternatively, if in the investigator's judgment it is in the best interest of the patient, cisplatin can be switched to carboplatin if the calculated CrCl is appropriate, and in consultation with the Sponsor.

- At the third occurrence of CrCl <50 mL/min, cisplatin should be discontinued. If in the investigator's judgment it is in the best interest of the patient, cisplatin can be switched to carboplatin if the calculated CrCl is appropriate, at the discretion of the investigator and in consultation with the Sponsor.

For patients receiving carboplatin, the scheduled dose of carboplatin may only be administered if the calculated CrCl is ≥40 mL/min:

- If CrCl falls to <40 mL/min, delay the start of that cycle for ≤21 days. In the interim, monitor renal function weekly and consider IV hydration. When CrCl improves to ≥40 mL/min, decrease carboplatin to DL -1 (Table 3).

- At the second occurrence of CrCl <40 mL/min, decrease carboplatin to DL -2 upon improvement of CrCl to ≥40 mL/min.

- At the third occurrence of CrCl <40 mL/min, carboplatin should be discontinued.

5.2.2 Timing of Dose Administration

All trial treatments will be administered on an outpatient basis.

Trial treatment should be administered beginning on Day 1 of each cycle after all procedures and assessments have been completed (time points listed in Section 6). Day 1 of each cycle should occur as scheduled (or in a window of ± 3 days for administrative reasons only). Etoposide must be administered on 3 consecutive days without interruption (Days 1, 2, and 3) in Cycles 1 to 4.

For subjects who experience disease progression, investigators may elect to continue trial treatment until confirmation of disease progression or may elect to interrupt treatment by deferring the decision to continue/discontinue treatment in the trial until confirmation of disease progression per modified RECIST 1.1 at least 28 days from the date of imaging

demonstrating disease progression. Subjects for whom disease progression is not confirmed on subsequent imaging may resume treatment. Please see Section 5.8 for other exceptions.

5.2.2.1 Pembrolizumab (or Saline Placebo)

Pembrolizumab or saline placebo will be administered first in the sequence of medications. Upon completion of the pembrolizumab or saline placebo infusion, premedication for the chemotherapy should be administered as per local SOC, followed by chemotherapy.

Pembrolizumab or saline placebo will be administered as a 30-minute IV infusion Q3W on Day 1 of each cycle. 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 to +10 minutes is permitted (ie, infusion time is 25 to 40 minutes).

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

5.2.2.2 Chemotherapy

Chemotherapy should be administered as described in the following subsections. Subjects are allowed to switch from cisplatin to carboplatin, if the subject becomes ineligible for further cisplatin therapy according to local guidelines and the investigator considers switching to carboplatin to be in the best interest of the subject.

5.2.2.2.1 Carboplatin

Carboplatin at a dose calculated to achieve an area under the plasma drug concentration time curve (AUC) of 5 will be administered as an IV infusion over approximately 60 minutes Q3W on Day 1 for 4 cycles. Carboplatin dose should not exceed 750 mg. AUC should be calculated using the Calvert formula:

- Total dose (mg) = (target AUC) × (CrCl + 25)
- The estimated CrCl in the Calvert formula should not exceed 125 mL/min
- Maximum carboplatin dose (mg) = target AUC 5 × (125 + 25)
  = 5 × 150
  = 750 mg

Creatinine clearance must be calculated using either the Cockcroft-Gault formula or another acceptable standard formula for estimating CrCl in mL/min based on serum creatinine:

- Men: [(140 - age (y)) × weight (kg)]/[72 × serum creatinine (mg/dL)]
- Women: [(140 - age (y)) × weight (kg)] × 0.85/[72 × serum creatinine (mg/dL)]

Note: Due to differences in serum creatinine units, sites may use either the standard Cockcroft-Gault formula or another acceptable standard formula used at their institution.

Dose may be rounded to the nearest 50 mg at the discretion of the investigator, and according to institutional standards.

Unless there is a change in weight >10%, the same dose of carboplatin can be used throughout the 4 cycles (provided there are no additional toxicities).

Additional premedications should be administered as per standard practice.

5.2.2.2.2 Cisplatin

Cisplatin 75 mg/m^2 will be administered as an IV infusion Q3W on Day 1 for 4 cycles. An infusion time of 60 minutes is recommended, but cisplatin may be administered over 30 to 180 minutes to accommodate local SOCs. Body surface area (BSA) will be obtained using the Dubois and Dubois or Mosteller formula. The BSA calculated on Cycle 1, Day 1 of therapy can be used throughout the 4 cycles, unless there is a change in weight >10%. Cisplatin will be given for up to 4 cycles. Additional premedications should be administered as per standard practice.

5.2.2.2.3 Etoposide

Etoposide 100 mg/m^2 will be administered as an IV infusion Q3W on Days 1, 2, and 3 of Cycles 1 to 4. Days 1, 2, and 3 must be consecutive days without interruption. An infusion time of 30 to 60 minutes is recommended, but etoposide may be administered over 30 to 120 minutes to accommodate local standards of care. Body surface area will be obtained using the Dubois and Dubois or Mosteller formula. The BSA calculated on Cycle 1, Day 1 of therapy can be used throughout the 4 cycles, unless there is a change in weight >10%. Additional premedications should be administered as per standard practice.

5.2.3 Trial Blinding

This is a double-blinded trial with respect to pembrolizumab and placebo treatment. The subject, the investigator, and Sponsor personnel or delegate(s) who are involved in the treatment administration or clinical evaluation of the subjects will be unaware of the treatment assignments. The chemotherapy agents will be open-label. Pembrolizumab will be supplied to the sites in an open label manner. The study site's unblinded pharmacist will obtain each subject's study identification number and study drug assignment from the interactive voice response system/integrated web response system (IVRS/IWRS) and prepare the solutions for infusion. The unblinded pharmacist will provide the investigative staff with ready-to-use blinded pembrolizumab or saline placebo infusion solutions, packaged identically in order to maintain the blinding, for administration at scheduled infusion visits. In addition to emergency unblinding for severe or life-threatening AEs with potential immunologic etiology, non-emergency unblinding to pembrolizumab versus placebo administration may occur on an individual subject basis and only after consultation with the Sponsor at the time of (1) centrally verified disease progression and subject has discontinued all study treatments or, (2) when the subject has discontinued all study treatments and a new anti-cancer treatment is going to be started. Non-emergency unblinding, only after

consultation and approval from the Sponsor, is implemented through interactive response technology (IRT) by following the instructions in the IRT site user manual.

Additionally, imaging data will be centrally reviewed by radiologists who are blinded to subject treatment assignment, and the allocation schedule will be blinded in the database, preventing aggregate analysis.

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

5.3 Randomization

Treatment 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 + EP or placebo + EP. Prior to randomization, the investigator's choice of platinum agent (cisplatin or carboplatin) will be documented in the IVRS/IWRS system.

5.4 Stratification

Treatment randomization will be stratified according to the following factors:

- Type of platinum therapy (carboplatin or cisplatin)
- Baseline ECOG performance status (0 or 1)
- Baseline LDH (≤ or >ULN)

5.5 Concomitant Medications/Vaccinations (Allowed & Prohibited)

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

5.5.1 Acceptable Concomitant Medications

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

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

All concomitant medications received within 28 days before the first dose of trial treatment and up to 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered more than 30 days after the last dose of trial treatment should be recorded for SAEs and events of clinical interest (ECIs) as defined in Section 7.2.

Colony-Stimulating Factors

The use of colony-stimulating factors (CSFs) is highly recommended as primary prophylaxis to reduce the risk of febrile neutropenia in this patient population, especially as many subjects have multiple co-morbidities and advanced disease. The American Society of Clinical Oncology guidelines for use of CSFs should be followed for this trial [112].

Antiemetic therapy

Antiemetic therapy should follow the Multinational Association of Supportive Care in Cancer guidelines [113].

5.5.2 Prohibited/Restricted Concomitant Medications

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

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Investigational agents other than pembrolizumab
- Surgery for tumor control
- Radiation therapy

  Note: Subjects are allowed to receive palliative radiotherapy for painful bone lesions. Targeted external beam irradiation should not be used in the primary lung field where assessment for tumor is indicated.

  Note: PCI is permitted in subjects achieving CR or PR after Cycle 4.

- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial (eg, measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine); seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed

- Systemic glucocorticoids for any purpose other than:
    - To modulate symptoms of an AE that is suspected to have an immunologic etiology
    - As required during and after PCI (subjects requiring chronic glucocorticoid use following PCI should be discontinued from study therapy)
    - As needed for the prevention of emesis (as outlined in Section 5.5.1)
    - For topical use or ocular use
    - Premedication for IV contrast allergies
    - For inhalation in the management of asthma or chronic obstructive pulmonary disease

Subjects who, in the assessment of 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.

Other medications that are prohibited in this trial are discussed in Section 5.1.3.

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

5.6 Rescue Medications & Supportive Care

No rescue or supportive medications are specified to be used in this trial.

5.6.1 Supportive Care Guidelines

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined along with the dose modification guidelines in Section 5.2.1.2.1, [Table 4]. Where appropriate, these guidelines include the use of oral or IV treatment with corticosteroids, as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab.

Note: If after evaluation of the event, it is determined not to be related to pembrolizumab, the investigator does not need to follow the treatment guidance. It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event.

Instructions regarding supportive care needed with the chemotherapeutic agents administered in this study can be found in the local product label for each agent. Infusion reactions and injection site reactions will be managed by the investigator according to local product labeling.

5.7 Diet/Activity/Other Considerations

5.7.1 Diet

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

5.7.2 Contraception

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

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

Chemotherapy can cause fetal harm if administered to pregnant women. Therefore, non-pregnant, non-breastfeeding women may be enrolled if they are considered of non-reproductive potential.

Female subjects will be considered of non-reproductive potential if they meet one of the following criteria:

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

- She had a hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy, or bilateral tubal ligation/occlusion at least 6 weeks prior to screening.

- She has a congenital or an acquired condition that prevents childbearing.

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

- Practice abstinence from heterosexual activity.
- Abstinence (relative to heterosexual activity) can be used as the sole method of contraception if it is consistently employed as the subject's preferred and usual lifestyle and if considered acceptable by local regulatory agencies and Ethics Review Committees (ERCs)/Institutional Review Boards (IRBs). Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
- Use (or have their partner use) acceptable contraception during heterosexual activity.

Acceptable methods of contraception are‡:

- Single method (one of the following is acceptable):
    - Intrauterine device (IUD)
    - Vasectomy of a female subject's male partner
    - Contraceptive rod implanted into the skin
- Combination method (requires use of 2 of the following):
    - Diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide)
    - Cervical cap with spermicide (nulliparous women only)
    - Contraceptive sponge (nulliparous women only)
    - Male condom or female condom (cannot be used together)
    - Hormonal contraceptive: oral contraceptive pill (estrogen/progestin pill or progestin-only pill), contraceptive skin patch, vaginal contraceptive ring, or subcutaneous contraceptive injection

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

Subjects should be informed that taking the trial medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the trial. In order to participate in

the trial, subjects of childbearing potential must adhere to the contraception requirement (described above) from the day of trial medication initiation (or 14 days prior to the initiation of trial medication for oral contraception) throughout the trial period up to 120 days after the last dose of pembrolizumab and up to 180 days after last dose of chemotherapeutic agents. If there is any question that a subject of childbearing potential will not reliably comply with the requirements for contraception, that subject should not be entered into the trial.

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 an SAE (eg, death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor. If a male subject impregnates his female partner, the study personnel at the site must be informed immediately and the pregnancy reported to the Sponsor and followed as described above and in Section 7.2.

5.7.3 Use in Nursing Women

It is unknown whether pembrolizumab is excreted in human milk. As 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

5.8.1 Discontinuation of Treatment

Discontinuation of trial treatment does not represent withdrawal from the trial.

As certain data on clinical events beyond treatment discontinuation may be/are important to the study, they must be collected through the subject's last scheduled follow-up, even if the subject has discontinued trial treatment. Therefore, all subjects who discontinue trial treatment prior to completion of the treatment period will still continue to participate in the trial as specified in Section 6.0 and Section 7.1.5.7.

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

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

- The subject or subject's legally acceptable representative requests to discontinue trial treatment.
- Confirmed radiographic disease progression, as outlined in Section 7.1.5 (exception if the Sponsor approves treatment continuation)

  Note: Subjects with new asymptomatic brain metastasis may be eligible to continue study treatment at the discretion of the investigator after consultation with the Sponsor. Section 7.1.2.7.6 provides details regarding eligibility requirements and subsequent radiographic assessments.
- Unacceptable AEs, as described in Section 7.2
- Any progression or recurrence of any malignancy, or any occurrence of another malignancy that requires active treatment
- Intercurrent illness other than another malignancy as noted above that prevents further administration of treatment
- Recurrent Grade 2 pneumonitis
- Recurrent Grade 3 diarrhea
- A confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements
- Investigator's decision to withdraw the subject
- Completion of 35 cycles of trial treatments (approximately 2 years)

Note: The number of treatments is calculated starting with the first dose. Subjects who stop trial treatment after receiving 35 doses of pembrolizumab or saline placebo may be eligible for the Second Course Phase (retreatment) if they progress after stopping trial treatment, provided they meet the requirements detailed in Section 7.1.5.5. Only subjects who were assigned to the pembrolizumab arm may be retreated in the Second Course Phase for up to an additional 17 cycles (approximately 1 year).

For subjects who are discontinued from trial treatment but continue to be monitored in the trial, all visits and procedures, as outlined in the trial flowchart, should be completed.

Discontinuation from trial treatment is "permanent." Once a subject is discontinued, he/she shall not be allowed to restart treatment.

5.8.2 Withdrawal from the Trial

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

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

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

5.9 Subject Replacement Strategy

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

5.10 Beginning and End of the Trial

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

5.11 Clinical Criteria for Early Trial Termination

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

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

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

Further recruitment in the trial or at 1 or more particular trial sites may be stopped due to insufficient compliance with the protocol, Good Clinical Practice (GCP), or other applicable regulatory requirements; procedure-related problems; or excessive number of discontinuations for administrative reasons.

6.0 TRIAL FLOW CHART

6.1 Initial Treatment Phase

	Screening Phase	Treatment Phase (3-Week Cycles)													End of Treatment	Follow-up		
Treatment Cycle	**Screening (Visit 1)**	**1**	**1**	**1**	**2**	**2**	**2**	**3**	**3**	**3**	**4**	**4**	**4**	**5-35**	**Discon[1]**	**Safety Follow-up[2]**	**PFS Follow-up Visits[3]**	**Survival Follow-up[4]**
Day (in Cycle)		**1**	**2&3**	**8**	**1**	**2&3**	**8**	**1**	**2&3**	**8**	**1**	**2&3**	**8**	**1**	**NA**	**NA**	**NA**	**NA**
Scheduling Window (Days):[5]	**-28 to -1**	**+ 3**		**± 1**	**± 3**		**± 1**	**± 3**		**± 1**	**± 3**		**± 1**	**± 3**	**At Time of Discon ± 3**	**30 Days From Last Dose + 7**	**Every 6 or 9 Weeks (± 7 days) per imaging schedule**	**Every 8 Weeks ± 7 days**
Administrative Procedures																		
Informed Consent	X																	
Informed Consent for Future Biomedical Research (optional)	X																	
Inclusion/Exclusion Criteria	X																	
Subject Identification Card	X																	
Demographics and Medical History	X																	
Prior and Concomitant Medications[6]	X	X		X	X		X	X		X	X		X	X	X	X	X	X
SCLC Disease Details	X																	
Obtain allocation number using IVRS		X																
Clinical Procedures/Assessments																		
Review Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[7]	X[7]	X[7]

	Screening Phase	Treatment Phase (3-Week Cycles)													End of Treatment	Follow-up		
Treatment Cycle	**Screening (Visit 1)**	**1**	**1**	**1**	**2**	**2**	**2**	**3**	**3**	**3**	**4**	**4**	**4**	**5-35**	**Discon[1]**	**Safety Follow-up[2]**	**PFS Follow-up Visits[3]**	**Survival Follow-up[4]**
Day (in Cycle)		**1**	**2&3**	**8**	**1**	**2&3**	**8**	**1**	**2&3**	**8**	**1**	**2&3**	**8**	**1**	**NA**	**NA**	**NA**	**NA**
Scheduling Window (Days):[5]	**-28 to -1**	**+ 3**		**± 1**	**± 3**		**± 1**	**± 3**		**± 1**	**± 3**		**± 1**	**± 3**	**At Time of Discon ± 3**	**30 Days From Last Dose + 7**	**Every 6 or 9 Weeks (± 7 days) per imaging schedule**	**Every 8 Weeks ± 7 days**
Full Physical Examination	X														X			
Directed Physical Examination		X		X	X		X	X		X	X		X	X				
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Height and Weight[8]	X	X			X			X			X			X	X	X		
12-Lead ECG	X																	
ECOG Performance Status	X[9]	X		X	X		X	X		X	X		X	X	X	X		
Prophylactic Cranial Irradiation[10]														X				
Laboratory Procedures/Assessments: Analysis Performed by Local Laboratory																		
Pregnancy Test – Urine or Serum β-HCG[11]	X																	
PT/INR[12]	X																	
CBC with Differential[12]	X	X		X	X		X	X		X	X		X	X	X	X		
Comprehensive Chemistry Panel[12]	X	X		X	X		X	X		X	X		X	X	X	X		
Urinalysis[12,13]	X													X		X		
Thyroid Function Tests[12,14]	X				X						X			X		X		
Hepatitis Serologies[12]	X																	

	Screening Phase	Treatment Phase (3-Week Cycles)													End of Treatment	Follow-up		
Treatment Cycle	**Screening (Visit 1)**	**1**	**1**	**1**	**2**	**2**	**2**	**3**	**3**	**3**	**4**	**4**	**4**	**5-35**	**Discon[1]**	**Safety Follow-up[2]**	**PFS Follow-up Visits[3]**	**Survival Follow-up[4]**
Day (in Cycle)		**1**	**2&3**	**8**	**1**	**2&3**	**8**	**1**	**2&3**	**8**	**1**	**2&3**	**8**	**1**	**NA**	**NA**	**NA**	**NA**
Scheduling Window (Days):[5]	**-28 to -1**	**+ 3**		**± 1**	**± 3**		**± 1**	**± 3**		**± 1**	**± 3**		**± 1**	**± 3**	**At Time of Discon ± 3**	**30 Days From Last Dose + 7**	**Every 6 or 9 Weeks (± 7 days) per imaging schedule**	**Every 8 Weeks ± 7 days**
Analysis Performed by Central Laboratory																		
Blood for Genetic Analysis[15]		X			X									C5D1 only	X			
Blood for RNA Analyses		X			X									C5D1 only	X			
Blood for Plasma Biomarker Analyses		X			X									C5D1 only	X			
Blood for Serum Biomarker Analyses		X			X									C5D1 only	X			
Tumor Tissue Collection																		
Archival or Newly Obtained Tissue Collection	X																	
Efficacy Measurements																		
CT/MRI Imaging of Chest, Abdomen, and Pelvis[16]	X							X[17]						X[17]	X[18]		X[17]	
MRI of Brain[19]	X							X[17,20]						X[17,21]	X[18]		X	
Bone Scan[22]	X																	
Survival Status[4]		<----------																---------->
Subsequent Anti-cancer Therapies															X	X	X	X

	Screening Phase	Treatment Phase (3-Week Cycles)													End of Treatment	Follow-up		
Treatment Cycle	**Screening (Visit 1)**	**1**	**1**	**1**	**2**	**2**	**2**	**3**	**3**	**3**	**4**	**4**	**4**	**5-35**	**Discon[1]**	**Safety Follow-up[2]**	**PFS Follow-up Visits[3]**	**Survival Follow-up[4]**
Day (in Cycle)		**1**	**2&3**	**8**	**1**	**2&3**	**8**	**1**	**2&3**	**8**	**1**	**2&3**	**8**	**1**	**NA**	**NA**	**NA**	**NA**
Scheduling Window (Days):[5]	**-28 to -1**	**+ 3**		**± 1**	**± 3**		**± 1**	**± 3**		**± 1**	**± 3**		**± 1**	**± 3**	**At Time of Discon ± 3**	**30 Days From Last Dose + 7**	**Every 6 or 9 Weeks (± 7 days) per imaging schedule**	**Every 8 Weeks ± 7 days**
Study Drug Administration[23]																		
Pembrolizumab or Saline Placebo[24]		X			X			X			X			X				
Carboplatin or Cisplatin[25]		X			X			X			X							
Etoposide[26]		X	X		X	X		X	X		X	X						
Patient Reported Outcomes[27]																		
EQ-5D-5L		X			X			X			X			X	X	X		
EORTC QLQ-C30		X			X			X			X			X	X	X		
EORTC QLQ-LC13		X			X			X			X			X	X	X		

1. 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 (ie, at the time of the mandatory Safety Follow up Visit), procedures required at both visits only need to be performed once.
2. 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. If the Discontinuation Visit occurs approximately 30 (± 3) days from last dose trial treatment the same procedures do not need to be repeated for the Safety Follow-up Visit.
3. Subjects who discontinue from the treatment phase prior to disease progression will continue to be followed in PFS follow-up until they experience disease progression or start a new antineoplastic therapy. 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.
4. Once the subject stops the imaging assessments (eg, for PD or starting a new antineoplastic therapy), the subject moves into the Survival Follow-up Phase and should be contacted by telephone approximately every 8 weeks to assess for survival status. Post-study antineoplastic treatments and the subject's response to them will also be collected. Updated survival status may be requested by the Sponsor at any time during the course of the study. Upon Sponsor notification, all participants who do not/will not have a scheduled study visit or study contact during the Sponsor defined time period will be contacted for their survival status (excluding participants that have a death event previously recorded).

5. In general, the window for Day 1 of each cycle is ±3 days unless otherwise noted. Days 1, 2, and 3 must be consecutive without interruption for Cycles 1 to 4; therefore, there is no visit window for Days 2 and 3 during the first 4 cycles. If treatment cycles are adjusted, all procedures except imaging will be completed according to the cycle number and not weeks on treatment; imaging will not be adjusted for delays in treatment cycles and will be performed per calendar schedule.
6. All concomitant medications received within 28 days before the first dose of trial treatment through the Safety Follow-up Visit (30 days after the last dose of trial treatment) should be recorded. Serious AEs that occur within 90 days after the end of treatment or before initiation of a non-study anticancer treatment must be documented and reported to the Sponsor immediately; after the Safety Follow-up Visit, all medications taken during the 14 days prior to an SAE and all medications taken to treat the SAE must be recorded as defined in Section 7.2. All non-study antineoplastic treatments should be documented.
7. See Section 7.2.3.1 for details on reporting timeframe for SAEs.
8. Height will be measured only at Visit 1. Only if there is a change in weight of >10%, should the dose of chemotherapy administered during Cycles 1 to 4 change.
9. ECOG for screening should be performed within 10 days prior to the first dose of trial treatment.
10. Subjects in either arm who achieve CR or PR after Cycle 4 may be offered PCI at the discretion of the treating investigator. See Section 7.1.2.6 for details.
11. For women of reproductive potential, a urine pregnancy test should be performed within 72 hours prior to first dose of trial treatment. A serum test can be considered if urine is not appropriate. Monthly pregnancy testing should be conducted as per local regulations where applicable.
12. Laboratory tests for screening are to be performed within 10 days prior to the first dose of trial treatment, with the exception of hepatitis serologies which may be performed within 28 days of the first dose of trial treatment. Testing for Hepatitis B and Hepatitis C should be performed as mandated by the local health authority. Starting with Cycle 1, laboratory safety tests must be conducted within 72 hours prior to the first dose of trial treatment in each cycle, with the exception of the thyroid function tests and LDH, which may be conducted up to 10 days prior to first dose of trial treatment. Laboratory results must be known prior to dosing.
13. Urinalysis is to be repeated every 6 cycles beginning at Cycle 6.
14. Thyroid tests are to be repeated every 2 cycles beginning at Cycle 2.
15. This sample should be drawn for planned analysis of the association between genetic variants in DNA and drug response. If there is either a documented law or regulation prohibiting collection, or if the IRB/IEC does not approve the collection of the sample for these purposes, then this sample will not be collected at that site. If the sample is collected, leftover extracted DNA will be stored for Future Biomedical Research if the subject signs the Future Biomedical Research consent. If the planned genetic analysis is not approved, but Future Biomedical Research is approved and consent is given, this sample will be collected for the purpose of Future Biomedical Research.
16. CT with contrast (preferred) of the chest, abdomen and pelvis is required for all subjects; non-contrast CT of the chest and MRI of the abdomen and pelvis may be used for subjects in whom iodinated contrast is contraindicated.
17. Tumor imaging to be performed every 6 weeks (42 [± 7] days) for the first 48 weeks of treatment from the date of randomization, then every 9 weeks (63 [± 7] days) subsequently until documented disease progression, or the start of new anti-cancer treatment. Refer to Section 7.1.2.7 for additional details. Imaging is to follow calendar days regardless of any delays in dosing. For patients treated beyond progression of disease as verified by BICR, the timing of imaging should continue from the date of randomization (every 6 weeks (42 [± 7] days) for the first 48 weeks, then every 9 weeks (63 [± 7] days) or at shorter intervals, as deemed necessary by the investigator).
18. If previous tumor imaging was obtained within 4 weeks prior to the date of discontinuation, then tumor imaging at treatment discontinuation is not mandatory.
19. MRI (strongly preferred) or CT with contrast of the brain at baseline for all subjects. For subjects without brain metastases at diagnosis, brain imaging is required prior to initiating PCI and as clinically indicated. For subjects with brain metastases at diagnosis that have undergone treatment, repeat brain imaging is to be performed at all post-baseline imaging assessments.
20. MRI (strongly preferred) or CT with contrast of the brain for subjects with metastases at diagnosis that have undergone treatment, repeat brain imaging is to be performed at all post-baseline imaging assessments.
21. MRI (strongly preferred) or CT with contrast of the brain for all subjects prior to initiating PCI.
22. Nuclear Medicine bone scan for all subjects, at baseline, to assess for bone lesions. Bone scan is to be repeated in patients with bone lesions at baseline who achieve a radiographic CR (to confirm osseous response) and as clinically indicated.
23. Study drug administration should begin on the day of randomization, but no later than 3 days after randomization.
24. Pembrolizumab 200 mg (or saline placebo) will be administered as a 30-minute IV infusion every 3 weeks (Q3W) for up to 35 cycles. During Cycles 1 to 4 pembrolizumab (or saline placebo) will be administered prior to administration of chemotherapy.
25. Carboplatin dosed to a target AUC of 5 and cisplatin 75 mg/m^2 will be administered as an IV infusion over approximately 60 minutes Q3W and over 30 to 180 minutes Q3W, respectively, on Day 1. Dose should be recalculated if there is a >10% weight change.

26. Etoposide 100 mg/m^2 will be administered as an IV infusion over 30 to 60 minutes (up to 120 minutes to accommodate local standards of care) Q3W on Days 1, 2, and 3. Days 1, 2, and 3 must be consecutive days without interruption. Dose should be recalculated if there is a >10% weight change.
27. PROs are completed every cycle for Cycles 1 to 9 while the subject is receiving study treatment, then every other cycle up to Cycle 17 (ie, Cycles 11, 13, 15, and 17). 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. 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: EQ-5D-5L, EORTC QLQ-C30, EORTC QLQ-LC13.

6.2 Second Course Treatment Phase

Second course retreatment subjects may receive up to 17 cycles (approximately 1 year) of pembrolizumab therapy. For subjects to be eligible for the Second Course Treatment Phase, it is necessary to fulfill conditions outlined in Section 7.1.5.5 and verify progression of disease by BICR.

	Treatment Phase		End of Treatment Phase	Follow-up Phase		
Treatment Cycle / Scheduled Time	**1[1]**	**2-17**	**Discontinuation Visit[2]**	**Safety Follow up Visit[3]**	**PFS Follow-up[4]**	**Survival Follow-up[5]**
Day in cycle		**1**	**NA**	**NA**	**NA**	**NA**
Scheduling Window (Days):[6]	**± 3**	**± 3**	**At Study Drug Discontinuation (± 3)**	**30 Days From Last Dose (+ 7)**	**Every 6 or 9 weeks per imaging schedule (± 7)**	**Every 8 Weeks ± 7**
Administrative Procedures						
Eligibility Criteria	X					
Prior and Concomitant Medications	X	X	X	X	X[7]	X[7]
Clinical Procedures / Assessments						
Review Adverse Events	X	X	X	X[8]	X[8]	X[8]
Full Physical Examination	X					
Directed Physical Examination		X	X	X		
Vital Signs and Weight	X	X	X	X		
ECOG Performance Status	X	X	X	X		
Laboratory Procedures / Assessments: analysis performed by local laboratory						
CBC with Differential[9]	X	X	X	X		
PT/INR[9]	X					
Comprehensive Chemistry Panel[9]	X	X	X	X		
Urinalysis[9,10]	X	X	X	X		
Thyroid Function Tests[9,11]	X	X	X	X		
Pregnancy Test – Serum or Urine[12]	X					

	Treatment Phase		End of Treatment Phase	Follow-up Phase		
Treatment Cycle / Scheduled Time	**1[1]**	**2-17**	**Discontinuation Visit[2]**	**Safety Follow up Visit[3]**	**PFS Follow-up[4]**	**Survival Follow-up [5]**
Day in cycle		**1**	**NA**	**NA**	**NA**	**NA**
Scheduling Window (Days):[6]	**± 3**	**± 3**	**At Study Drug Discontinuation (± 3)**	**30 Days From Last Dose (+ 7)**	**Every 6 or 9 weeks per imaging schedule (± 7)**	**Every 8 Weeks ± 7**
Efficacy Measurements						
CT/MRI Imaging of Chest, Abdomen, and Pelvis[13,14]	X	X	X	X	X	
MRI of Brain[14,15]	X	X	X	X	X	
Bone Scan[14,16]	X					
Subsequent Antineoplastic Therapy Status			X	X	X	X
Survival Status[5]	<--->					
Study Drug Administration						
Pembrolizumab[17]	X	X				

1. Procedures and assessments completed at the time of withdrawal from the main study may be used, as appropriate, for the start of the Second Course Phase of the study. Otherwise, assessments and procedures are to be performed on Day 1 and prior to the first dose of trial treatment for each cycle, unless specified.
2. 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 (ie, at the time of the mandatory Safety Follow-up Visit), procedures required at both visits only need to be performed once.
3. 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. If the Discontinuation Visit occurs approximately 30 (± 3) days from last dose trial treatment the same procedures do not need to be repeated for the Safety Follow-up Visit.
4. Subjects who discontinue from the treatment phase prior to disease progression will continue to be followed in PFS follow-up until they experience disease progression or start a new antineoplastic therapy. 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.
5. Once the subject stops the imaging assessments for this protocol (eg, for PD or starting a new antineoplastic therapy), the subject moves into the Survival Follow-up and should be contacted by telephone every 8 weeks to assess for survival status. Post-study treatments and the subject's response to them will also be collected. Updated survival status may be requested by the Sponsor at any time during the course of the study. Upon Sponsor notification, all participants who do not/will not have a scheduled study visit or study contact during the Sponsor defined time period will be contacted for their survival status (excluding participants that have a death event previously recorded).
6. In general, the window for each visit is ±3 days unless otherwise noted. If treatment cycles are adjusted all procedures except imaging will be completed according to the Cycle number and not weeks on treatment; imaging will not be adjusted for delays in treatment cycles and will be performed per calendar schedule. The visit windows for follow-up are indicated in days.

7. After the Safety Follow-up Visit, record all medications taken during the 14 days prior to an SAE and all medications taken to treat an SAE as defined in Section 7.2. All non-study antineoplastic treatments should be documented.
8. See Section 7.2.3.1 for details on reporting timeframe for SAEs.
9. Laboratory tests for determining eligibility for retreatment are to be performed within 10 days prior to the first dose of pembrolizumab. Starting with Cycle 1 Day 1, laboratory safety tests must be conducted within 72 hours prior to first dose of trial treatment in each cycle, with the exception of the thyroid function tests and LDH which may be conducted up to 10 days prior to first dose of trial treatment. Laboratory results, with the exception of thyroid function tests and LDH, must be known prior to dosing.
10. Urinalysis is to be performed every 6 cycles.
11. Thyroid tests are to be repeated every 2 cycles beginning at Cycle 2.
12. For women of reproductive potential, a urine pregnancy test should be performed within 72 hours prior to first dose of trial treatment. A serum test can be considered if urine is not appropriate. Monthly pregnancy testing should be conducted as per local regulations where applicable.
13. CT with contrast (preferred) of the chest, abdomen and pelvis is required for all subjects; non-contrast CT of the chest and MRI of the abdomen and pelvis may be used for subjects in whom iodinated contrast is contraindicated.
14. Tumor imaging to be performed within 28 days prior to restarting treatment with pembrolizumab. Tumor response assessment is required every 6 weeks (42 [± 7] days) for the first 26 weeks of the Second Course Phase, then every 9 weeks (63 [± 7] days) until the subject starts a non-study cancer therapy. Refer to site imaging manual for additional details. Additional imaging at Discontinuation Visit and Safety Follow-up Visit is not required provided that previous imaging assessments have been performed per schedule. Additional imaging after study drug discontinuation is not required for subjects who start a non-study cancer therapy. Refer to Section 7.1.2.7 for additional details.
15. MRI (strongly preferred) or CT with contrast of the brain at baseline for all subjects. For subjects without brain metastases at diagnosis, brain imaging is required as clinically indicated. For subjects with brain metastases at diagnosis that have undergone treatment, repeat brain imaging is to be performed at all post-baseline imaging assessments.
16. Nuclear medicine bone scan for all subjects, at baseline, to assess for bone lesions. Bone scan is to be repeated in subjects with bone lesions at baseline who achieve a radiographic CR (to confirm osseous response) and as clinically indicated.
17. Pembrolizumab can be administered for up to 17 cycles.

7.0 TRIAL PROCEDURES

7.1 Trial Procedures

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

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

7.1.1 Administrative Procedures

7.1.1.1 Informed Consent

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

7.1.1.1.1 General Informed Consent

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

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

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

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

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

7.1.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

The investigator or qualified designee will explain the Future Biomedical Research consent to the subject, answer all of his/her questions, and obtain written informed consent before performing any procedure related to 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. At the time of treatment allocation/randomization, site personnel will add the treatment/randomization number to the Subject Identification Card.

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

7.1.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee. The medical history will collect all active conditions and any condition diagnosed within the prior 10 years that the investigator considers to be clinically significant. Details regarding the disease for which the subject has enrolled in this trial will be recorded separately and not listed as medical 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 28 days before starting the trial treatment. Any treatment provided for the disease for which the subject has enrolled in this trial will be recorded separately and not listed as a prior medication.

7.1.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the subject during the trial through the Safety Follow-up visit. In addition, new medications started during the Second Course Phase through the respective Safety Follow-up visit should be recorded. All medications related to reportable SAEs and ECIs should be recorded as defined in Section 7.2.

7.1.1.6 Assignment of Screening Number

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

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

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

7.1.1.7 Assignment of Treatment/Randomization Number

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

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

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

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

Administration of trial medication(s) will be witnessed by the investigator and/or trial staff. The total volume of pembrolizumab infused will be compared to the total volume prepared to determine compliance with each dose administered. Start and stop times of drug administration should be recorded in the source documents.

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 (Section 6.0) 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 4.0 (see Section 12.4). Toxicities will be characterized in terms including seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

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

7.1.2.2 Physical Examination

7.1.2.2.1 Full Physical Examination

The investigator or qualified designee will perform a full physical examination during the screening period before the Initial Treatment Phase, and on Cycle 1, Day 1 of the Second Course Treatment Phase. Clinically significant abnormal findings should be recorded as medical history. The time points for full physical examination are described in the Trial Flow Chart (Section 6). After the first dose of trial treatment new clinically significant abnormal findings should be recorded as AEs.

7.1.2.2.2 Directed Physical Examination

For cycles/visits that do not require a full physical examination per the Trial Flow Chart (Section 6), the investigator or qualified designee will perform a directed physical examination as clinically indicated prior to trial treatment administration and at other times according to the Trial Flow Chart (Section 6). New clinically significant abnormal findings should be recorded as AEs.

7.1.2.3 Vital Signs

Vital signs include temperature, pulse, respiratory rate, weight, and blood pressure. The investigator or qualified designee will take vital signs at screening, prior to the administration of each dose of trial treatment, during the follow-up phase, and at other visits as specified in the Trial Flow Chart (Section 6.0). Height will be measured at Visit 1 only.

7.1.2.4 12-Lead Electrocardiogram

A standard 12-lead electrocardiogram 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 Performance Status

The investigator or qualified designee will assess ECOG status (see Section 12.3) at screening, prior to each cycle of trial treatment and during the Follow-up period as specified in the Trial Flow Chart (Section 6).

7.1.2.6 Prophylactic Cranial Irradiation

Subjects in either arm who achieve CR or PR after Cycle 4 may be offered PCI at the discretion of the treating investigator. Imaging of the brain must occur after the completion of 4 cycles of trial treatment, just prior to PCI.

Subjects selected to receive PCI may receive up to 25 Gy in 10 fractions (or the biologic equivalent), as tolerated by the subject. If given, PCI must begin within 6 weeks (preferably within 2 to 4 weeks) after the last dose of study medication in Cycle 4. Study medication may continue during PCI; however, if it is necessary to suspend study treatment, dosing must be restarted no later than 2 weeks after completion of PCI. Steroids can be administered, as required, during and after PCI.

7.1.2.7 Tumor Imaging and Assessment of Disease

The process for image collection and transmission to BICR can be found in the Site Imaging Manual. The same imaging technique regarding modality and use of contrast should be used consistently throughout the trial. Imaging schedule should follow calendar days and should not be adjusted for cycle delays.

Screening (baseline) imaging:

- CT with IV and oral contrast (preferred) of the chest, abdomen and pelvis for all subjects, or non-contrast CT of the chest and magnetic resonance imaging (MRI) of the abdomen and pelvis with IV gadolinium for subjects in whom iodinated contrast is contraindicated
- MRI (strongly preferred) or CT with contrast (when MRI is medically contraindicated) of the brain for all subjects
- Nuclear medicine bone scan for bone lesions

Post baseline imaging:

- CT or MRI of the chest, abdomen and pelvis, consistent with the method used at baseline
- Imaging of the brain, consistent with the method used at baseline:
    - At all post-baseline visits for subjects with baseline brain metastases
    - For subjects who will undergo PCI, should be performed prior to PCI
    - If clinically indicated

- Nuclear medicine bone scan for bone lesions:
    - If clinically indicated
    - In subjects with bone lesions at baseline who achieve a radiographic CR to confirm osseous response

Local site investigator/radiology assessment based on RECIST 1.1 (modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ) will be used to determine subject eligibility. All scheduled images for all study subjects from the sites will be submitted to the BICR. In addition, all other imaging (including all modalities) obtained at an unscheduled time point to determine disease progression, as well as supplemental imaging obtained for other reasons that captures radiologic progression, should be submitted to the BICR.

The BICR will review images for the verification of progression following the first radiologic evidence of PD based on local investigator assessment. Expedited verification of radiologic PD by the BICR will be communicated to the study site and Sponsor (See Section 7.1.2.7.2). Details can be found in the Site Imaging Manual.

7.1.2.7.1 Initial Tumor Imaging

Initial tumor imaging at screening must be performed within 28 days prior to the date of randomization. The site investigator/local radiology reviewer must review screening images to confirm the subject has measurable disease per RECIST 1.1 (modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ). The screening images must be submitted to the BICR for retrospective review.

Tumor imaging via CT performed as part of routine clinical management (prior to informed consent form signature) is acceptable for use as screening tumor imaging if they are of diagnostic quality, are performed within 28 days prior to the date of randomization, and can be assessed by BICR.

7.1.2.7.2 Tumor Imaging During the Trial

The first on-trial imaging assessment should be performed at 6 weeks (42 ± 7 days) from the date of randomization. Subsequent tumor imaging should be performed every 6 weeks (42 ± 7 days) for the first 48 weeks of treatment, then every 9 weeks (63 [± 7] days), or more frequently if clinically indicated. Timing of tumor imaging should follow calendar days and should not be adjusted for delays in cycle starts. (Note: the date imaging is performed is the date of the imaging, not the date the images are reviewed.) Imaging should continue to be performed until disease progression verified by BICR (unless site PI elects to continue treatment and follow irRECIST), the start of a non-study anti-cancer treatment, withdrawal of consent, or death, whichever occurs first. Supplemental imaging must be submitted to the central imaging vendor if it shows evidence of progression or if it is used to support a determination of PR or CR.

Per RECIST 1.1 (modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ), PR and CR should be confirmed by a repeat tumor imaging assessment not less than 4 weeks from the date the response was first documented. The tumor imaging for confirmation of response may be performed at the next scheduled tumor imaging (ie, 6 or 9 weeks later), whichever is clinically indicated. Subjects will then return to regular scheduled imaging every 6 or 9 weeks, starting with the next scheduled imaging time point. Subjects who obtain confirmatory imaging do not need to undergo the next scheduled tumor imaging if it is <4 weeks later; tumor imaging may resume at the subsequent scheduled imaging time point.

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

7.1.2.7.3 End of Treatment and Follow-up of Tumor Imaging

For subjects who discontinue trial treatment, tumor imaging should be performed at the time of treatment discontinuation. If previous tumor imaging was obtained within 4 weeks prior to the date of discontinuation, then tumor imaging at treatment discontinuation is not required. For subjects who discontinue trial treatment due to documented disease progression, this is the final required tumor imaging.

In subjects who discontinue trial treatment without documented disease progression, every effort should be made to continue monitoring disease status by tumor imaging using the same imaging schedule and modality used while on treatment (every 6 weeks [42 ± 7 days] for the first 48 weeks after randomization, then every 9 weeks [63 ± 7 days]) to monitor disease status until the start of non-study anticancer treatment, disease progression, death, or the end of the trial, whichever occurs first.

7.1.2.7.4 Second Course (Retreatment) Phase Tumor Imaging

Tumor imaging must be performed within 28 days prior to restarting treatment with pembrolizumab in the Second Course Phase. Disease progression must be verified by BICR using RECIST 1.1 (modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ).

The first on study imaging assessment of the Second Course Phase should be performed at 6 weeks (42 [± 7] days) after the first dose of trial treatment in that phase. Subsequent tumor imaging should be performed every 6 weeks (42 [± 7] days) for the first 26 weeks of that phase, then every 9 weeks (63 [± 7] days), or more frequently if clinically indicated.

Per irRECIST (Section 7.1.2.7.6), if tumor imaging shows initial PD, tumor assessment should be repeated ≥4 weeks later in order to confirm PD. Investigators and subjects have the option to continue treatment while awaiting radiologic confirmation of progression. Subjects who have confirmatory imaging are not required to complete the next scheduled tumor imaging if it is <4 weeks later and may wait until the following scheduled imaging time point if clinically stable.

Imaging should continue to be performed until disease progression, the start of a non-study anticancer treatment, withdrawal of consent, death, or notification by the Sponsor, whichever occurs first. Disease progression may be confirmed ≥4 weeks after the first tumor imaging indicating PD in clinically stable subjects.

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

In subjects who discontinue trial treatment without documented disease progression, every effort should be made to continue monitoring disease status by radiologic imaging every 6 weeks (42 [± 7] days) for the first 26 weeks after the first dose of trial treatment in that phase, then every 9 weeks (63 [± 7] days) until either the start of a non-study anticancer treatment, disease progression, death, or the end of the trial, whichever occurs first.

7.1.2.7.5 RECIST 1.1 Assessment of Disease

RECIST 1.1 (see Section 12.5) will be applied by the BICR as the primary measure for assessment of tumor response, date of disease progression, and as a basis for all protocol guidelines related to disease status (eg, discontinuation of study therapy). Although RECIST 1.1 references a maximum of 5 target lesions in total and 2 per organ, Merck allows a maximum of 10 target lesions in total and 5 per organ, if clinically relevant, to enable a broader sampling of tumor burden. Initial tumor imaging showing site-assessed PD should be submitted to the BICR immediately. The site will be notified of the result of BICR tumor imaging assessment using RECIST 1.1, ie, verification of progression. Figure 2 illustrates the imaging flow involving verification of PD for clinically stable subjects.

7.1.2.7.6 irRECIST Assessment of Disease

To account for the unique tumor response seen with immunotherapeutic drugs, irRECIST is RECIST 1.1 adapted as described below. The site investigator/local radiology review will use irRECIST to assess tumor response and progression, and to make treatment decisions. This data will be collected in the clinical database. Treatment efficacy based on irRECIST will be evaluated retrospectively as an exploratory endpoint.

When feasible, subjects should not be discontinued until progression is confirmed by the local site investigator/radiology assessment. This allowance to continue treatment despite initial radiologic PD takes into account the observation that some subjects can have a

transient tumor flare during the first few months after the start of immunotherapy, and then experience subsequent disease response. Subjects that are deemed clinically unstable are not required to have repeat tumor imaging for confirmation of PD. Tumor flare includes any of the following scenarios:

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

In subjects who have shown initial evidence of radiologic disease progression as assessed by BICR per RECIST 1.1 (modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ), it is at the discretion of the principal investigator whether to continue a subject on study treatment until repeat imaging is obtained (using irRECIST for subject management, see Table 8 and Figure 2). This clinical judgment decision by the site investigator should be based on the subject's overall clinical condition, including performance status, clinical symptoms, and laboratory data. Subjects may receive study treatment and tumor assessment should be repeated ≥4 weeks later in order to confirm PD by irRECIST per site assessment. **Clinical stability** is defined as the following:

- Neurologically stable without the need for steroids (for subjects with brain metastasis);
- Absence of symptoms and signs indicating clinically significant progression of disease, including worsening of laboratory values;
- No decline in ECOG performance status;
- Absence of rapid progression of disease; and
- Absence of progressive tumor at critical anatomical sites (eg, cord compression) requiring urgent alternative medical intervention (including immediate need for surgery or WBRT in the case of new brain metastases).

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

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

Disease progression will be considered to be "not confirmed" at repeat imaging if ALL of the following occur (as assessed by irRECIST):

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

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

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

- Target lesion sum of diameters reaches or remains ≥20% and ≥5 mm absolute increase compared to nadir
- Non-target disease shows unequivocal progression, or the non-target disease resulting in initial PD is qualitatively worse
- New lesions appear for the first time, or the new lesions resulting in initial PD are increased in size or number

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

Note: If a subject has confirmed radiographic progression (ie, 2 scans at least 4 weeks apart demonstrating PD) per irRECIST, but the subject is achieving a clinically meaningful benefit, and there is no further increase in the tumor burden at the confirmatory tumor imaging, an exception to continue treatment may be considered following consultation with the Sponsor (see Section 7.1.5.6 for details). In this case, if treatment is continued, tumor imaging should continue to be performed following the intervals as outlined in the Trial Flowchart (Section 6.0) and be submitted to the BICR.

If a subject develops a new brain metastasis during treatment, the following steps will be taken:

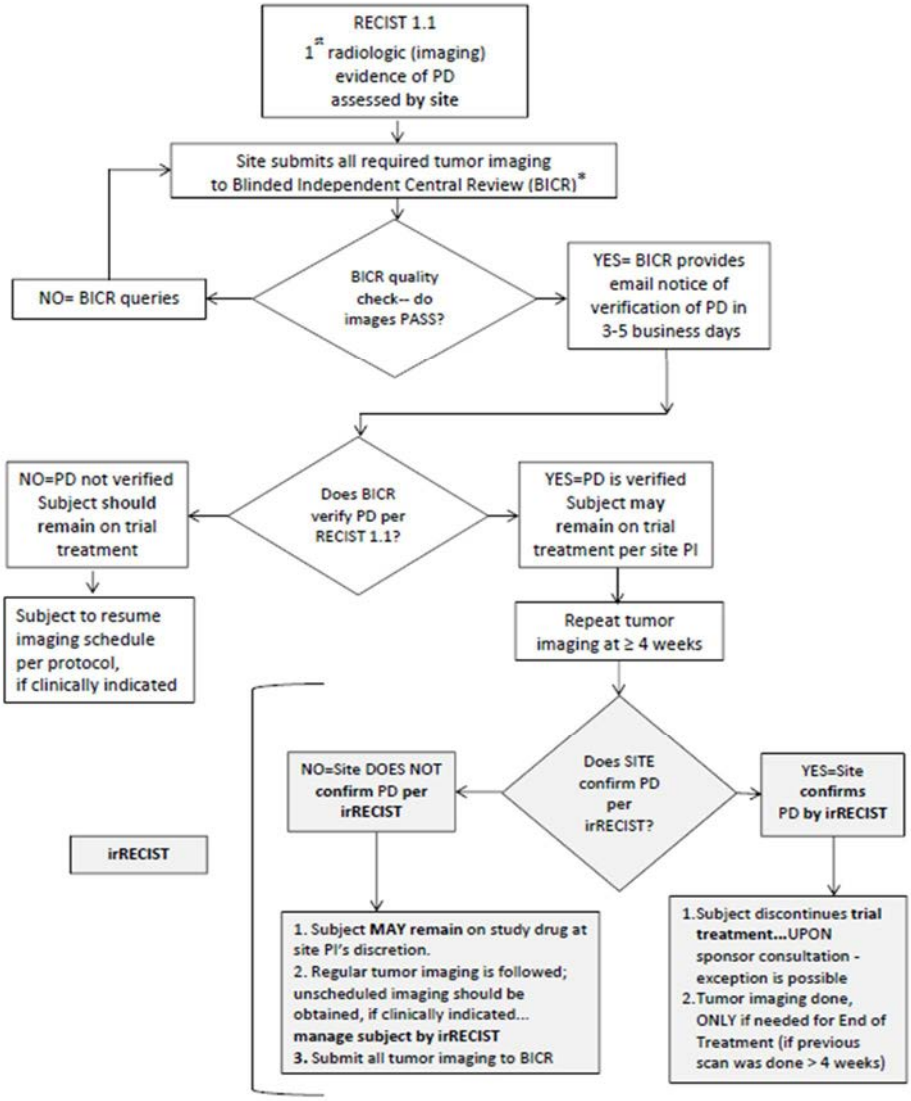
- Subjects with symptomatic brain metastases will be removed from study treatment.
- Subjects with asymptomatic brain metastases (no need for steroids, no symptoms and signs indicating clinically significant progression of disease, no decline in ECOG performance status) can continue on study treatment under the following conditions:
    - If no immediate WBRT, both systemic lesions and brain lesions can be followed by irRECIST.
    - If immediate WBRT is chosen, the brain lesions will be non-evaluable for irRECIST.
    - Brain MRI will be required at each subsequent image assessment.

Additional details about irRECIST are referenced in the Merck Imaging Tip Sheet for RECIST 1.1 and irRECIST.

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

	Clinically Stable		Clinically Unstable	
	Imaging	**Treatment**	**Imaging**	**Treatment**
First radiologic evidence of PD by RECIST 1.1 (modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ), which has been verified by the BICR	Repeat imaging at ≥4 weeks at site to confirm PD	May continue study treatment at the local site investigator's discretion while awaiting confirmatory tumor imaging by site by irRECIST.	Repeat imaging at ≥4 weeks to confirm PD per physician discretion only (Imaging should be reviewed by radiology as soon as possible.)	Discontinue treatment
Repeat tumor imaging confirms PD irRECIST at the local site	No additional imaging required	Discontinue treatment (exception is possible upon consultation with Sponsor)	No additional imaging required	N/A
Repeat tumor imaging shows SD, PR or CR by irRECIST at the local site	Continue regularly scheduled imaging assessments	Continue study treatment at the local site investigator's discretion	Continue regularly scheduled imaging assessments	May restart study treatment if condition has improved and/or clinically stable per investigator's discretion. Next tumor imaging should occur according to the regular imaging schedule outlined in the protocol

Abbreviations: BICR=blinded independent central review; CR=complete response; irRECIST=immune-related Response Evaluation Criteria in Solid Tumors; N/A=not applicable; PD=progressive disease; PR=partial response; SD=stable disease



Abbreviations: BICR=blinded independent central review, irRECIST=immune-related Response Evaluation Criteria in Solid Tumors, PD=progressive disease, PI=principal investigator, RECIST=Response Evaluation Criteria in Solid Tumors

*If subject is clinically stable, may continue study treatment at the local site investigator's discretion while awaiting verification of PD per RECIST 1.1 by BICR and/or confirmatory tumor imaging by site by irRECIST.

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

7.1.2.8 Tumor Tissue Collection: PD-L1 Status

Participation in this trial will be dependent upon supplying tumor tissue for PD-L1 testing from locations not radiated prior to biopsy. Subjects whose submitted tissue is not evaluable for PD-L1 status can still be eligible to participate in the study.

All subjects should submit either a newly obtained core or excisional biopsy or archival tissue (fine needle aspiration [FNA], endobronchial ultrasound [EBUS], guided transbronchial needle aspiration [TBNA], cell pellets, cytology, and blood smears are not adequate for both archival and new tissue samples) to a central laboratory for characterization of PD-L1 status prior to treatment allocation.

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

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

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

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

7.1.3 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below. The total amount of blood/tissue to be drawn/collected over the course of the trial (from pre-trial to post-trial visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per subject can be found in the Laboratory Manual. Refer to the Trial Flow Chart (Section 6.0) for the timing of laboratory assessments.

7.1.3.1 Clinical Laboratory Evaluations

Clinical laboratory tests are specified in Table 9.

Table 9 Clinical Laboratory Tests

Hematology	Hematocrit, hemoglobin, platelet count, WBC (total and differential), RBC, absolute lymphocyte count, absolute neutrophil count
Chemistry	Albumin, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, bicarbonate (only required if done as part of standard of care by local laboratory), calcium, chloride, creatinine, glucose, phosphorus, potassium, sodium, total bilirubin, direct bilirubin (if total bilirubin >ULN), total protein, blood urea nitrogen or urea (one or the other should be collected per institutional standard; both of these laboratory tests are not required), LDH[a]
Thyroid Function Tests[a]	Total T3 or free T3 (T3 is preferred; if not available, free T3 may be tested), FT4, and TSH
Coagulation Parameters	PT/INR
Hepatitis Serologies[b]	HbsAg, HCV RNA (qualitative), Anti-HCV
Pregnancy test	If the urine test is not negative, then a serum test must be performed.
Urinalysis	Blood, glucose, protein, specific gravity Microscopic exam should be performed if abnormal results are noted

Abbreviations: FT4=free thyroxine; HbsAg=hepatitis B surface antigen; HCV=hepatitis C virus; LDH=Lactate dehydrogenase; PT=prothrombin time; RBC=red blood cells; T3=triiodothyronine; TSH=thyroid-stimulating hormone; ULN=upper limit of normal; WBC=white blood cells.

[a] If the local laboratory is unable to perform these tests, the site should submit the sample to the central laboratory for testing. Details are provided in the Laboratory Manual.

[b] Hepatitis C antibody testing is allowed in countries where HCV RNA is not part of standard of care. Testing for Hepatitis B and Hepatitis C should be performed as mandated by the local health authority.

For both the Initial Treatment Phase and the Second Course Phase:

- Screening laboratory tests should be performed within 10 days prior to the first dose of trial treatment, with the exception of the hepatitis serologies which may be performed within 28 days of the first dose of trial treatment in the Initial Treatment Phase only. Testing for hepatitis B and hepatitis C should be performed as mandated by the local health authority.

- Clinical laboratory tests must be conducted within 72 hours prior to first dose of trial treatment in each cycle, with the exception of laboratory tests performed by the central lab, which may be conducted up to 10 days prior to first dose of trial

treatment. Laboratory test results must be reviewed by the investigator or qualified designee and found to be acceptable prior to administration of first trial treatment.

- For laboratory tests performed by the central laboratory, any results not available prior to dosing must be reviewed by the investigator or qualified designee within 48 hours of receipt and found to be acceptable prior to subsequent administration of trial treatment.

- During the Initial Treatment Phase, laboratory tests will also be performed at the Day 8 Visit of each cycle. Results must be reviewed by the investigator or qualified designee within 48 hours of receipt.

- Unresolved abnormal laboratory test results that are drug-related AEs should be followed until resolution.

Laboratory tests do not need to be repeated after the end of treatment if laboratory test results are within the normal range.

7.1.3.2 Pharmacokinetic/Pharmacodynamic Evaluations

Pembrolizumab

The accumulation of robust PK and anti-drug antibodies (ADA) data has allowed for the adequate characterization of the clinical pharmacology of pembrolizumab across indications. Therefore, upon approval of Amendment 07, each site is to stop the collection of PK and ADA samples for all subjects. Blood samples for PK and ADA collected prior to Amendment 07 may be stored. Analysis will be performed only if required.

Exploratory drug-drug interaction analysis

The accumulation of robust PK data has allowed for adequate characterization of the potential for drug-drug interactions between pembrolizumab and chemotherapy. Therefore, upon approval of protocol amendment 06, each site is to stop the collection of PK samples for etoposide only. Blood samples for etoposide PK collected prior to protocol amendment 06 may be stored. Analysis will be performed only if required.

Patient-reported Outcomes

For PROs, the EQ-5D-5L, EORTC QLQ-C30, and EORTC QLQ-LC13 questionnaires will be administered by trained study site personnel and completed electronically by the subjects themselves.

It is strongly recommended that electronic PROs are administered prior to drug administration, AE evaluation, and disease status notification. The electronic PROs are completed in the following order: EQ-5D-5L first, then EORTC QLQ-C30, and lastly, the EORTC QLQ-LC13 at the time points specified in the Trial Flow Charts and briefly summarized below.

The EQ-5D-5L, EORTC QLQ-C30, and EORTC QLQ-LC13 are completed every cycle for Cycles 1 to 9, then every other cycle up to Cycle 17 (ie, Cycles 11, 13, 15, and 17) while the subject is receiving study treatment. Patient-reported outcomes will also be obtained at the treatment discontinuation visit and 30-day Safety Follow-up visit.

7.1.3.3 Planned Genetic Analysis Sample Collection

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

7.1.3.4 Future Biomedical Research Samples

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

- DNA for future research
- Leftover RNA
- Leftover plasma and serum from biomarker analyses
- Leftover tumor

7.1.4 Other Procedures

7.1.4.1 Withdrawal/Discontinuation

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

When a subject discontinues/withdraws from participation in the trial, all applicable activities scheduled for the 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.

Withdrawal From Future Biomedical Research

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

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

7.1.4.2 Subject Blinding/Unblinding

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

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

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

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

7.1.4.3 Calibration of Critical Equipment

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

Critical Equipment for this trial includes:

None

7.1.5 Visit Requirements

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

7.1.5.1 Screening

Within 28 days prior to randomization, potential subjects will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5.1. Visit requirements are outlined in the Trial Flow Chart (Section 6.0). Screening procedures may be repeated.

Written consent must be obtained prior to performing any protocol-specific procedure. Results of a test performed prior to the subject signing consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame. Screening procedures are to be completed within 28 days prior to the first dose of trial treatment except for the following:

- Laboratory tests are to be performed within 10 days prior to the first dose of trial treatment with the exception of hepatitis serologies testing, which may be done up to 28 days prior to the first dose of trial treatment. Testing for hepatitis B and hepatitis C should be performed as mandated by the local health authority.

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

- Tumor imaging must be performed within 28 days prior to randomization.

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

7.1.5.2 Treatment Period Visits

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

7.1.5.3 Post-treatment Visits

7.1.5.3.1 Safety Follow-up Visit

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

AE to Grade ≤1 or until beginning of a new antineoplastic therapy, whichever occurs first. Serious AEs that occur within 90 days of the end of treatment or before initiation of a non-study anticancer treatment should also be followed and recorded; additionally, all medications taken during the 14 days prior to an SAE and all medications taken to treat the SAE must be recorded.

Subjects who are eligible for retreatment with pembrolizumab may have up to 2 Safety Follow-up visits, the first after the Initial Treatment Phase and the second after the Second Course Phase.

7.1.5.3.2 Progression-free Survival Follow-up Visits

Subjects who discontinue trial treatment for a reason other than disease progression will move into the PFS Follow-up Phase and should be assessed as follows to monitor disease status by imaging depending on the trial phase:

- Initial Treatment Phase: tumor imaging every 6 weeks (42 [± 7] days) for the first 48 weeks after randomization, then every 9 weeks (63 [± 7] days) per the imaging schedule.

- Second Course Phase: tumor imaging every 6 weeks (42 [± 7] days) for the first 26 weeks from the date of the first dose of trial medication in this phase, then every 9 weeks (63 [± 7] days) per the imaging schedule.

The Sponsor may request survival status to be assessed at additional time points during the course of the study (not to exceed approximately every 8 weeks). Every effort should be made to collect information regarding disease status until the start of new anti-cancer therapy, disease progression, death, end of trial. Information regarding post-trial anticancer treatment will be collected if new treatment is initiated.

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

7.1.5.3.3 Survival Follow-up

Once a subject experiences PD or starts a non-study anti-cancer therapy, the subject will move into the Survival Follow-up Phase and should be contacted by telephone approximately every 8 weeks to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first. Post-study treatments and the subject's response to them will also be collected.

7.1.5.4 Survival Status

To ensure current and complete survival data is available at the time of database locks, updated survival status may be requested during the course of the study by the Sponsor. For example, updated survival status may be requested prior to. But not limited to, an external DMC review, interim and/or final analyses. Upon Sponsor notification, all participants who do not/will not have a scheduled study visit or study contact during the Sponsor defined time

period will be contacted for their survival status (excluding participants that have previously recorded a death event in the collection tool).

7.1.5.5 Second Course Phase

Subjects who have stable disease (SD), PR, or CR after receiving 35 pembrolizumab treatments may be eligible for retreatment with up to an additional 17 cycles (approximately 1 year) of pembrolizumab treatment. This retreatment is termed the Second Course Phase of this trial and will only be available upon consultation with the Sponsor if the trial remains open and if the subject meets the following conditions:

- Had SD, PR, or CR and stopped treatment after completion of 35 administrations (approximately 2 years) of pembrolizumab in the Initial Treatment Phase. (Consultation with the Sponsor will be needed in those cases where pembrolizumab was stopped for reasons other than disease progression or intolerability before 35 cycles.)

  AND

- Experienced a BICR-verified radiographic disease progression by modified RECIST 1.1 after stopping initial treatment, and

  - No new anticancer treatment was administered after the last dose of trial treatment, and

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

  - The trial is ongoing.

Treatment assignment will be unblinded only for those subjects who meet all criteria for the Second Course Phase. Subjects in the saline placebo arm are not eligible for the Second Course Phase.

Procedures and assessments for the Second Course Phase will be initiated once radiographic disease progression by modified RECIST 1.1 has been determined by the investigator and verified by BICR, and the subject has met the criteria listed above. All procedures and assessments completed at the time of withdrawal from the Initial Treatment Phase may be used, as appropriate, for the start of the Second Course Phase of the study. Procedures and assessments must be completed within 28 days after radiographic progression by modified RECIST 1.1.

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

Visit requirements are outlined in the Trial Flow Chart (Section 6.2). Survival assessments and their respective entries into the database may be required more frequently around the time of the projected analyses (eg, DMC reviews, interim analyses).

Specific procedure-related details are provided above in Section 7.1.

7.1.5.6 Continued Treatment Following Verified Progressive Disease

Subjects who are deemed by the investigator to be benefiting clinically despite documented PD assessed by BICR using RECIST 1.1 (modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ), may remain on study and continue receiving the originally assigned trial treatment for a total of 35 cycles. Continued post-PD treatment is optional and will be determined at the discretion of the investigator (in consultation with the Sponsor).

Subjects who meet the following criteria will be eligible for continued post-PD treatment:

- Documentation of PD will be defined as BICR assessment.
- AEs (except alopecia and peripheral neuropathy) due to therapy must have improved to NCI CTCAE 4.0 Grade ≤1.
- If a subject is unstable as a result of a new or progressing brain metastasis(es), the subject will not be eligible for continued treatment.
- ECOG Performance Status of 0 or 1.
- Subject must not have received any non-study systemic anti-cancer therapies.
- Subject has adequate organ function as indicated by the laboratory assessments listed in Section 5.1.2.

Visit requirements are outlined in the Trial Flow Chart (Section 6.1). Survival assessments and their respective entries into the database may be required more frequently around the time of the projected analyses (eg, DMC reviews, interim analyses). Specific procedure-related details are provided above in Section 7.1.

7.1.5.7 Discontinued Subjects Continuing to be Monitored in the Trial

Subjects who discontinue from the treatment phase prior to disease progression will continue to be followed in PFS follow-up until they experience disease progression or start a new antineoplastic therapy. Subjects with an AE of Grade >1 will be further followed until the resolution of the AE to Grade ≤1 or until beginning of a new antineoplastic therapy, whichever occurs first.

Date of disease recurrence or metastatic progression, start and stop dates of subsequent anti-cancer treatments, and reasons for treatments should be recorded in the appropriate

eCRF. Survival assessments and their respective entries into the database may be required more frequently around the time of the projected analyses (eg, DMC reviews, interim analyses). For subjects who die during the follow-up period, the date and cause of death should be recorded in the appropriate eCRF.

7.2 Assessing and Recording Adverse Events

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

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

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

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

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

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

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

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

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

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

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

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

7.2.2 Reporting of Pregnancy and Lactation to the Sponsor

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

Pregnancies and lactations that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the subject to be excluded from the trial or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure. Pregnancies and lactations that occur from the time of treatment allocation/randomization through 120 days following cessation of Sponsor's product, or 180 days after last dose of chemotherapeutic agents, or 30 days following cessation of trial treatment if the subject initiates new anticancer therapy, whichever is earlier, must be reported by the investigator. All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

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

7.2.3 Immediate Reporting of Adverse Events to the Sponsor

7.2.3.1 Serious Adverse Events

An SAE is any AE occurring at any dose or during any use of Sponsor's product that:

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

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

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

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

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

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

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

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

All subjects with SAEs must be followed up for outcome.

7.2.3.2 Events of Clinical Interest

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

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

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

Events of clinical interest for this trial include:

- 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.

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

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

7.2.3.3 Protocol-Specific Exceptions to Serious Adverse Event Reporting

Efficacy endpoints as outlined in this section will not be reported to the Sponsor as described in Section 7.2.3.

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

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

7.2.4 Evaluating Adverse Events

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

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

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

Table 10 Evaluating Adverse Events

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

V4.0 CTCAE Grading	**Grade 1**	**Mild; asymptomatic or mid symptoms; clinical or diagnostic observations only; intervention not indicated.**
	Grade 2	**Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.**
	Grade 3	**Severe or medically significant but not immediately life-threatening; hospitalization or prolongation or hospitalization indicated; disabling; limiting self-care ADL.**
	Grade 4	**Life threatening consequences; urgent intervention indicated.**
	Grade 5	**Death related to AE**
Seriousness	A serious adverse event is any adverse event occurring at any dose or during any use of Sponsor's product that:	
	†**Results in death**; or	
	†**Is life threatening; or** places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred (Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.); or	
	†**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or	
	†**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not a serious adverse event. A pre-existing condition is a clinical condition that is diagnosed prior to the use of a Merck product and is documented in the patient's medical history.); or	
	†**Is a congenital anomaly/birth defect** (in offspring of subject taking the product regardless of time to diagnosis);or	
	Is a new **cancer** (that is not a condition of the study) **(**although not serious per ICH definition, is reportable to the Sponsor within 24 hours to meet certain local requirements); **or**	
	Is an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event for collection purposes. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours.	
	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	
Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the adverse event cause the Sponsor's product to be discontinued?	
Relationship to Sponsor's Product	Did the Sponsor's product cause the adverse event? The determination of the likelihood that the Sponsor's product caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the adverse event based upon the available information. **The following components are to be used to assess the relationship between the Sponsor's product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Sponsor's product caused the adverse event (AE):	
	Exposure	Is there evidence that the subject was actually exposed to the Sponsor's product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
	Time Course	Did the AE follow in a reasonable temporal sequence from administration of the Sponsor's product? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors

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

7.2.5 Sponsor Responsibility for Reporting Adverse Events

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

7.3 TRIAL GOVERNANCE AND OVERSIGHT

Executive Oversight Committee

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

7.3.1 Data Monitoring Committee

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

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

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

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

8.0 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, changes are made to primary and/or key secondary hypotheses, or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with ICH Guideline E9). Changes to exploratory or other non-confirmatory analyses made after the protocol has been finalized, but prior to the conduct of any analysis, will be documented in a supplemental statistical analysis plan (sSAP) and referenced in the Clinical Study Report (CSR) for the study. The PRO analysis plan will also be included in the sSAP.

8.1 Statistical Analysis Plan Summary

Key elements of the Statistical Analysis Plan (SAP) are summarized below. The comprehensive plan is provided in Section 8.2 through Section 8.12.

Analysis Strategy for Key Efficacy Endpoints

Study Design Overview	This is a Phase 3, randomized, multi-site, double-blind study of 1L pembrolizumab+EP versus saline placebo+EP in ES-SCLC (KEYNOTE-604)
Treatment Assignment	Approximately 430 subjects were planned to be randomized in a 1:1 ratio to receive pembrolizumab+EP or saline placebo+EP. The stratification factors used for this study are a) cisplatin vs carboplatin, b) ECOG status (0 vs 1), and, c) LDH at baseline (≤ vs > ULN). This is a double-blind study. By the time of the current amendment, 453 subjects were randomized for the study.
Analysis Populations	Efficacy: Intention-to-Treat (ITT) Safety: All Subjects as Treated (ASaT)
Primary Endpoints	1) PFS as assessed by BICR RECIST 1.1 modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ 2) OS
Secondary Endpoints	3) ORR as assessed by BICR per RECIST 1.1 modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ 4) DOR as assessed by BICR per RECIST 1.1 modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ 5) AEs
Statistical Methods for Key Efficacy Analyses	The primary hypotheses will be evaluated by comparing 1L pembrolizumab+EP to 1L saline placebo+EP based on PFS as assessed by BICR RECIST 1.1 modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ and OS in subjects with ES-SCLC using a stratified log-rank test. Hazard ratios (HRs) will be estimated using a stratified Cox regression model. Event rates over time will be estimated within each treatment group using the Kaplan-Meier method.
Statistical Methods for Key Safety Analyses	The analysis of safety results will follow a tiered approach. There are no Tier 1 safety parameters in this trial. All safety parameters are considered either Tier 2 or Tier 3. Tier 2 parameters will be assessed via point estimates with 95% CIs provided for between-group comparisons; only point estimates by treatment group are provided for Tier 3 safety parameters. The between-treatment difference will be analyzed using the Miettinen and Nurminen method.

Interim and Final Analyses	Two interim analyses are planned in this study. Results will be reviewed by the external DMC. Details are provided in Section 8.7 – Interim Analyses. • Interim analysis 1 o Timing: To be performed at approximately 18 months from study start, where study start is the date on which the first subject was randomized. ORR p-value from the first interim analysis (IA1) may be evaluated for statistical significance if PFS and OS null hypotheses are rejected at IA1 or at a later analysis time. o Purpose: Interim PFS and OS analyses to demonstrate superiority of pembrolizumab+EP over saline placebo+EP.
	• Interim analysis 2 o Timing: To be performed at approximately 22 months from study start. Purpose: Final PFS analysis and interim OS analysis to demonstrate superiority of pembrolizumab+EP over saline placebo+EP.
	• Final analysis o Timing: To be performed after a minimum of 294 deaths are observed or approximately 31 months after first subject enrolled, whichever occurs later. o Purpose: Final analysis of OS to demonstrate superiority of pembrolizumab+EP over saline placebo+EP.
Multiplicity	The family-wise type I error rate for this study is strongly controlled at 2.5% (one-sided) for the hypothesis testing of PFS, OS, and ORR. The multiplicity strategy will follow the graphical approach of Maurer and Bretz [114] as described in Section 8.8, with 0.6% and 1.9% alpha initially allocated to the PFS and OS hypotheses, respectively. Group sequential methods will be used to allocate alpha between the interim and final analyses for PFS and OS endpoints. Further details of the interim analysis strategy can be found in Section 8.7 and Section 8.8.
Sample Size and Power	The planned sample size is approximately 430 subjects. The actual sample size is 453 subjects. For PFS, based on 387 events, the study has 95.6% power to detect a HR of 0.65 (pembrolizumab+EP vs saline placebo+EP) at α=0.6% (one-sided). For OS, based on a minimum of 294 events, the study has at least 94.4% power to detect a HR of 0.65 (pembrolizumab+EP vs saline placebo+EP) at α=1.9% (one-sided).

8.2 Responsibility for Analyses/In-house Blinding

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

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

Planned interim analyses are described in Section 8.7. Participant-level unblinding will be restricted to an external unblinded statistician and scientific programmer performing the interim analysis, who will have no other responsibilities associated with the study.

An external DMC will be convened to review accumulating safety data to provide an opportunity to terminate the study early if there are concerns regarding safety. Treatment-level results at the interim analyses will be provided by the external unblinded statistician to the DMC. The DMC will also review the unblinded efficacy results at the planned interim analyses. The DMC responsibilities and review schedules will be outlined in the DMC charter. The recommendation of the DMC will be communicated to the Sponsor EOC and, in the event of a recommendation to halt the trial early due to safety concerns, to the appropriate regulatory agencies. If the DMC recommends modifications to the design of the protocol or discontinuation of the study, the EOC may be unblinded to results at the treatment level in order to act on these recommendations. Participant-level unblinding to support regulatory filing, should one occur before the end of the study, will be restricted to a designated Sponsor/MSD team, who will have no other responsibilities associated with the study.

The extent to which individuals are unblinded with respect to the results will be documented. Additional logistical details, revisions to the above plan, and data monitoring guidance will be provided in the DMC Charter.

8.3 Hypotheses/Estimation

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

8.4 Analysis Endpoints

8.4.1 Efficacy Endpoints

Primary

Progression-free Survival – RECIST 1.1 assessed by BICR

Progression-free survival is defined as the time from randomization to the first documented disease progression as assessed by BICR per RECIST 1.1 modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ or death due to any cause, whichever occurs first. See Section 8.6.1 for definition of censoring.

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 analysis will be censored at the date of last known contact.

Secondary

Objective Response Rate – RECIST 1.1 assessed by BICR

Objective response rate is defined as the proportion of subjects who have a CR or a PR. Responses are based on confirmed assessments by BICR per RECIST 1.1 modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ.

Duration of Response – RECIST 1.1 assessed by BICR

For subjects who demonstrate CR or PR, DOR is defined as the time from first documented evidence of CR or PR until disease progression or death due to any cause, whichever occurs first. DOR will be assessed by BICR per RECIST 1.1 modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ.

8.4.2 Safety Endpoints

Safety measurements are described in Section 4.2.3.3 and Section 7. Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs, laboratory tests, and vital signs. Safety parameters to be analyzed include, but are not limited to, AEs, SAEs, fatal AEs, and laboratory changes. Furthermore, specific events will be collected and designated as ECIs as described in Section 7.2.3.

8.5 Analysis Populations

8.5.1 Efficacy Analysis Populations

The analyses of primary efficacy endpoints are based on the intention-to-treat (ITT) population (ie, subjects will be included in the treatment group to which they are randomized). Details on the approach to handling missing data are provided in Section 8.6.

8.5.2 Safety Analysis Populations

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

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

8.6 Statistical Methods

8.6.1 Statistical Methods for Efficacy Analyses

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

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

8.6.1.1 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 (based on the stratification factors defined in Section 5.4). A stratified Cox proportional hazard model with Efron's method of tie handling will be used to assess the magnitude of the treatment difference (ie, the hazard ratio [HR]) between the treatment arms. The HR and its 95% CI from the stratified Cox model with Efron's method of tie handling and with a single treatment covariate will be reported. The stratification factors used for randomization (See Section 5.4) will be applied to both the stratified log-rank test and the stratified Cox model.

Since disease progression is assessed periodically, PD can occur any time in the time interval between the last assessment where PD was not documented and the assessment when PD is documented. For the primary analysis, for the subjects who have PD, the true date of disease progression will be approximated by the date of the first assessment at which PD is objectively documented as assessed by BICR per RECIST 1.1 modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ, regardless of discontinuation of study drug. Death is always considered as a confirmed PD event.

In order to evaluate the robustness of the PFS endpoint per modified RECIST 1.1 by central imaging vendor, we will perform 2 sensitivity analyses with a different set of censoring rules. The first sensitivity analysis is the same as the primary analysis except that data for any subject who misses more than one disease assessment (with or without a subsequent death or progression) are censored at the last disease assessment prior to missing visits. The second sensitivity analysis is the same as the primary analysis except that it considers discontinuation of treatment or initiation of an anticancer treatment subsequent to discontinuation of study-specified treatments, whichever occurs later, to be a PD event for subjects without documented PD or death. If a subject meets multiple criteria for censoring, the censoring criterion that occurs earliest will be applied. The censoring rules for primary and sensitivity analyses are summarized in Table 11.

Table 11 Censoring Rules for Primary and Sensitivity Analyses of Progression-free Survival

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
No PD and no death; ≥2 consecutive missed disease assessments	Censored at last disease assessment	Censored at last disease assessment prior to ≥2 consecutive missed visits	Censored at last disease assessment
PD or death documented after ≤1 missed disease assessment	Progressed at date of documented PD or death	Progressed at date of documented PD or death	Progressed at date of documented PD or death
PD or death documented at any time after ≥2 missed disease assessments	Progressed at date of documented PD or death	Censored at last disease assessment prior to the ≥2 missed disease assessment	Progressed at date of documented PD or death

8.6.1.2 Overall Survival

The non-parametric Kaplan-Meier method will be used to estimate the survival curves. The treatment difference in survival will be assessed by the stratified log-rank test (based on the stratification factor defined in Section 5.4). A stratified Cox proportional hazard model with Efron's method of tie handling will be used to assess the magnitude of the treatment difference (ie, the HR). The HR and its 95% CI from the stratified Cox model with a single treatment covariate will be reported. The stratification factors used for randomization (See Section 5.4) will be applied to both the stratified log-rank test and the stratified Cox model. Restricted Mean Survival Time (RMST) method may be conducted for OS to account for the possible non-proportional hazards effect.

Since subjects in the placebo+EP arm are expected to discontinue from the study earlier compared to subjects in the pembrolizumab arm because of earlier onset of PD and may switch to another anti PD-1 treatment following confirmation of PD, adjustment for the effect of crossover on OS may be performed based on recognized methods, (eg, the Rank Preserving Structural Failure Time (RPSFT) model proposed by Robins and Tsiatis [115]), based on an examination of the appropriateness of the data to the assumptions required by the method used.

8.6.1.3 Objective Response Rate

The ORR is defined as the proportion of subjects who achieve a best objective response of PR or CR.

Stratified Miettinen and Nurminen's method will be used for comparison of ORR between the treatment groups. The difference in ORR and its 95% CI from the stratified Miettinen and Nurminen method with strata weighting by sample size will be provided. The same stratification factors used for randomization (see Section 5.4) will be used as stratification factors in the analysis.

8.6.1.4 Duration of Response

For subjects who demonstrate CR or PR, DOR is defined as the time from first documented evidence of CR or PR until disease progression or death due to any cause, whichever occurs first. Censoring rules for DOR are summarized in Table 12. DOR will be assessed by BICR per RECIST 1.1 modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ.

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

Table 12 Censoring Rules for Duration of Response

Situation	Date of Progression or Censoring	Outcome
No progression nor death, no new anti-cancer therapy initiated	Last adequate disease assessment	Censor (non-event)
No progression nor death, new anti-cancer therapy initiated	Last adequate disease assessment before new anti-cancer therapy initiated	Censor (non-event)
Death or progression after ≥2 consecutive missed disease assessments	Last adequate disease assessment prior to ≥2 missed adequate disease assessments	Censor (non-event)
Death or progression after ≤1 missed adequate disease assessments	Progressive disease or death	End of response (Event)
Note: A missed disease assessment includes any assessment that is not obtained or is considered inadequate for evaluation of response.		

A summary of the primary analysis strategy for the primary and secondary efficacy endpoints is provided in Table 13.

Table 13 Efficacy Analysis Methods for Primary and Secondary Efficacy Endpoints

Endpoint/Variable (Description, Time Point)	Statistical Method	Analysis Population	Missing Data Approach
Primary Analyses:			
PFS (RECIST 1.1*) by BICR	Testing: Stratified Log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT	Censored according to rules in Table 11
OS	Testing: Stratified Log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT	Censored at last known alive date
Secondary Analyses:			
ORR (RECIST 1.1*) by BICR	Testing: Stratified Miettinen and Nurminen method	ITT	Subjects with missing data are considered non-responders
DOR (RECIST 1.1*) by BICR	Summary statistics using Kaplan-Meier method	All responders in ITT	Non-responders are excluded in analysis
*As assessed by BICR per RECIST 1.1 modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ			

8.6.2 Statistical Methods for Safety Analyses

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

The analysis of safety results will follow a tiered approach (Table 14). The tiers differ with respect to the analyses that will be performed. Safety parameters or AEs 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.

Adverse events of special interest (AEOSIs) that are immune-mediated or potentially immune-mediated are well documented and will be evaluated separately; however, these events have been characterized consistently throughout the pembrolizumab clinical development program and determination of statistical significance is not expected to add value to the safety evaluation. Further, pembrolizumab added to platinum doublets studied thus far have not been found to impact safety, and in an ongoing Phase 1 clinical trial, the chemotherapeutic regimen used here with pembrolizumab has not led to increased toxicity

(NCT02402920). Additionally, there are no known AEs associated with subjects with SCLC for which determination of a p-value is expected to impact the safety assessment. For these reasons, there are no events of interest that warrant inferential testing. Therefore, there are no Tier I events in this study.

Adverse experiences (specific terms as well as system organ class terms) that are not pre-specified as Tier-1 endpoints will be classified as belonging to "Tier 2" or "Tier 3", based on the number of events observed. Membership in Tier 2 requires that at least 10% of subjects in any treatment group exhibit the event; all other AEs and predefined limits of change will belong to Tier 3.

The threshold of at least 10% was chosen for membership in Tier 2 because subjects enrolled in this study are in critical condition and usually experience various AEs of similar types regardless of treatment, events reported less frequently than in 10% of subjects would obscure the assessment of the overall safety profile and add little to the interpretation of potentially meaningful treatment differences. In addition, Grades 3 to 5 AEs (≥5% of subjects in one of the treatment arms) and SAEs (≥5% of subjects in one of the treatment arms) will be considered Tier 2 events. For Tier 2 events, 95% CIs will be provided for between-treatment differences in the percentage of subjects with events; these analyses will be performed using the Miettinen and Nurminen method [116], an unconditional, asymptotic method. Because many 95% CIs may be provided without adjustment for multiplicity, the CIs should be regarded as a helpful descriptive measure to be used in safety review, not a formal method for assessing the statistical significance of the between-treatment differences.

For laboratory parameters, the number and percentage of subjects with increases from baseline in laboratory test toxicity grades based on the highest post-baseline toxicity grade and shift of toxicity grade from baseline to the worst post-baseline toxicity grade will be summarized by treatment arm.

Table 14 Analysis Strategy for Safety Parameters

Safety Tier	Safety Endpoint	95% CI for Treatment Comparison	Descriptive Statistics
Tier 2	Any AE (≥10% of subjects in one of the treatment arms)	X	X
	Any Grades 3 to 5 AE (≥5% of subjects in one of the treatment arms)	X	X
	Any serious AE (≥5% of subjects in one of the treatment arms)	X	X
Tier 3	Any AE		X
	Any change from baseline results (laboratory tests)		X
Abbreviations: AE=adverse event, CI=confidence interval			

8.6.3 Summaries of Baseline Characteristics and Demographics

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.

8.7 Interim Analyses

Two interim efficacy analyses are planned for this study.

- The (IA1) will be performed approximately 18 months from study start. PFS and OS will be evaluated at IA1. ORR p-value from IA1 may be evaluated for statistical significance if PFS and OS null hypotheses are rejected at IA1 or at a later analysis time.

- The second interim analysis (IA2) is the final formal analysis of PFS. It will be performed at approximately 22 months after first subject enrolled. The second interim analysis evaluation of OS will be performed at this time.

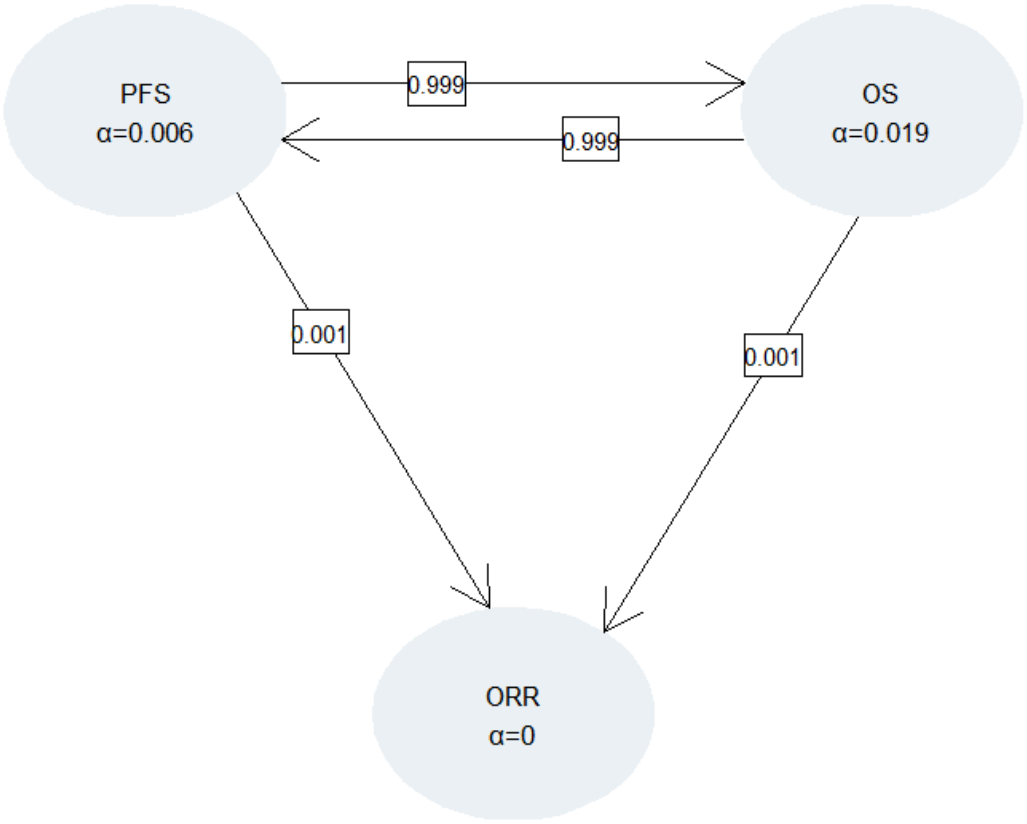
- The final analysis will evaluate OS only. It is planned when a minimum of 294 deaths have been observed or approximately 31 months after first subject enrolled, whichever occurs later.

In addition to the formal efficacy analyses, the DMC will conduct regular safety monitoring, the timing of which is specified in the DMC charter. Decisions to stop the trial early will be based on DMC recommendations with review by the EOC.

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

8.8 Multiplicity

The trial uses the graphical method of Maurer and Bretz [114] to control multiplicity for multiple hypotheses as well as interim analyses. Figure 3 shows the initial one-sided α allocation for each hypothesis in the ellipse representing the hypothesis. The weights for reallocation from each hypothesis to the others are represented in the boxes on the lines connecting hypotheses.



Note: If both PFS and OS null hypotheses are rejected, the reallocation strategy allows testing of ORR at alpha=0.025.

Figure 3 Multiplicity Graph for Type I Error Control

Progression-free Survival

If the null hypothesis for OS is rejected, Figure 3 shows that its α=0.019 is essentially fully reallocated to PFS hypothesis testing. Thus, the PFS null hypothesis may be tested at α=0.006 or at α=0.025. For PFS hypotheses, the targeted number of events at the final PFS analysis will be 387. A Lan-DeMets O'Brien-Fleming spending function will be used for information fraction-based alpha-spending to generate the group sequential design. The bounds provided in Table 15 are based on the assumption that the number of events at IA1 and IA2 are 332 and 387, respectively. The actual boundaries and the nominal alpha level will be determined based on the actual number of PFS events observed at the time of the analyses and from the overall alpha level after any potential alpha-shifting as the result of a successful OS analysis. The final PFS analysis at IA2 will use the remaining Type I error not spent at the IA1, regardless of the actual number of PFS events observed. The p-value bound at the final PFS analysis will be calculated by considering the correlation between the test statistics as determined by the actual number of PFS events at IA1 and the final PFS analysis at IA2. The bounds given in Table 15 will be adjusted accordingly.

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

Analysis	Targeted Analysis Time	Cumulative alpha spent[1]	Efficacy Bars[1]
IA1 (86%[2])	Approximately 18 months from study start[3]	0.003	• (One-sided) p-value <0.003 • Observed HR <~ 0.74
IA2 (100%[2])	Approximately 22 months from study start[3]	0.006	• (One-sided) p-value <0.0051 • Observed HR <~ 0.77

[1] Nominal alpha, boundaries, and cumulative alpha are based on the assumption that 332 and 387 events are at IA1 and IA2, respectively. The p-value boundaries will be updated at the time of analyses based on actual number of PFS events.

[2] Percentage of expected number of events at final analysis targeted at interim analysis.

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

Note that if the α-reallocation from OS hypothesis testing occurs at the final analysis after hypothesis testing for PFS has been completed, the previously computed PFS test statistic for the PFS final analysis may be re-evaluated based on the updated bounds.

Overall Survival

The OS hypothesis may be tested at α=0.019 (initially allocated α) or at α=0.025 (if PFS null hypothesis is rejected) following the multiplicity strategy as outlined in Figure 3. The bounds and boundary properties for OS hypothesis testing at the initial alpha level are demonstrated in Table 16. The alpha spending at each interim analysis is determined using a Lan-DeMets O'Brien-Fleming spending function, and the information fraction (ratio of the actual number of events at the interim analysis relative to a targeted 294 events at the final analysis). The final analysis will use the remaining Type I error not spent at earlier analyses, regardless of the number of events observed at the final analysis. The p-value bounds at second interim and final analysis will be calculated by considering the correlation between the test statistics as determined by the actual number of OS events at the previous and current analysis. The p-value bounds at each analysis time may also be updated after potential alpha-shifting as the result of a successful PFS analysis.

Table 16 Efficacy Boundaries and Properties for Overall Survival Analyses

Analysis	Targeted Analysis Time	Cumulative alpha spent[1]	Efficacy Bars[1]
IA1 (60%[2])	Approximately 18 months from study start[3]	0.0024	• (One-sided) p-value <0.0024 • Observed HR <~ 0.65
IA2 (76%[2])	Approximately 22 months from study start[3]	0.0071	• (One-sided) p-value <0.0064 • Observed HR <~ 0.72
FA (100%[2])	A minimum of 294 deaths observed in 2 arms or approximately 31 months from study start, whichever occurs later[3]	0.019	• (One-sided) p-value <0.0167 • Observed HR <~ 0.78

[1] Nominal alpha, boundaries, and cumulative alpha are based on the number of deaths expected assuming the projected number of events using protocol assumptions, ie, 175, 224, and 294 at IA1, IA2 and final analysis, respectively. The p-value boundaries will be updated at the time of analyses based on actual number of deaths.

[2] Percentage of expected number of events at final analysis targeted at interim analysis.

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

The DMC has responsibility for assessment of overall risk: benefit. When prompted by safety concerns, the DMC can request corresponding efficacy data. DMC review of efficacy data to assess the overall risk: benefit to study participants will not require a multiplicity adjustment typically associated with a planned efficacy IA. However, to account for any multiplicity concerns raised by the DMC review of unplanned efficacy data when prompted by safety concerns, a sensitivity analysis for OS adopting a conservative multiplicity adjustment will be pre-specified in the sSAP.

Objective Response Rate

The trial does not allocate initial alpha to ORR. ORR will be formally tested only if the hypotheses for PFS and OS are significant. The testing of ORR will be based on the first 352 subjects enrolled in the trial. If the null hypotheses for OS and PFS are rejected at IA1 or at a time later than IA1, the p-value of ORR from the IA1 analysis will be compared to an α-level of 0.025. Power at the possible α-level as well as the approximate treatment difference required to reach the bound (ΔORR) are shown in Table 17, assuming underlying 50% and 70% response rates in the control and experimental groups, respectively.

Table 17 Possible Alpha-levels and Approximate ORR Difference Required to Demonstrate Efficacy for ORR

α	~ΔORR	Power
0.025	0.1002	0.9719

8.9 Sample Size and Power Calculations

Four hundred and thirty subjects were planned to be randomized in 1:1 ratio into pembrolizumab+EP and the saline placebo+EP arms. By the time of the current amendment, 453 subjects were enrolled for this study.

The final PFS analysis for the study will occur about 22 months from study start. If 387 PFS events occur by the time of the final PFS analysis, the study will have a power of 96% approximately to demonstrate a HR of 0.65 on PFS at initially allocated α=0.006.

The final OS analysis will occur when at least 294 events have occurred or approximately 31 months from study start, whichever occurs later. With a minimum of 294 events at the time of final analysis, the study has at least 94% power to demonstrate a HR of 0.65 on OS at initially allocated α=0.019.

The above power calculations for OS and PFS are based on the following assumptions: 1) 453 subjects were enrolled over 14.5 months following the actual enrollment pattern; 2) median PFS is 4.3 months in the control arm and HR is 0.65; 3) median OS is 10 months in the control arm and HR is 0.65; 4) The exponential dropout rates assumed for OS and PFS are 1% per month.

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

8.10 Subgroup Analyses and Effect of Baseline Factors

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

- Stratification factors
    - Platinum chemotherapy (cisplatin, carboplatin)
    - LDH (≤ULN, >ULN)
    - ECOG Performance Scale (0, 1)
- Age category (<65, ≥65 years)

- Sex (female, male)
- Race (white, all others)
- Smoking status (former, current)
- Brain/liver metastasis status at diagnosis (yes, no)
- Region (East Asia, non-East Asia)
- Sites of metastasis at diagnosis (<3, ≥3)
- PD-L1 expression positive (TPS<1% vs ≥1%, CPS <1 vs ≥1)

8.11 Compliance (Medication Adherence)

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

8.12 Extent of Exposure

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

9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.1 Investigational Product

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

Clinical Supplies will be provided by the Sponsor as summarized in Table 18. All other supplies not indicated in Table 18 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.

Table 18 Product Descriptions

Product Name & Potency	**Dosage Form**	**Source/Additional Information**
Pembrolizumab 25 mg/mL (MK-3475)	Solution for Infusion	Provided centrally by the Sponsor
Carboplatin	Solution for Infusion	Provided centrally by the Sponsor or locally by the trial site, subsidiary, or designee. Product is not IMP
Cisplatin	Solution for Infusion	Provided centrally by the Sponsor or locally by the trial site, subsidiary, or designee Product is not IMP
Etoposide	Solution for Infusion	Provided centrally by the Sponsor or locally by the trial site, subsidiary, or designee Product is not IMP
Abbreviations: IMP=investigational medicinal product		

All supplies indicated in Table 18 will be provided per the "Source/Additional Information" column depending on local country operational requirements.

Any commercially available product not included in Table 18 will be provided by the trial site, subsidiary or designee. Every attempt should be made to source these supplies from a single lot/batch number. The trial site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product as per local guidelines unless otherwise instructed by the Sponsor.

9.2 Packaging and Labeling Information

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

Open-label pembrolizumab will be provided in 2 vial kits. Open-label carboplatin, cisplatin, and etoposide will be provided as single-vial kits.

9.3 Clinical Supplies Disclosure

The pembrolizumab treatment in the trial is blinded but supplies are provided open label; therefore, an unblinded pharmacist or qualified trial site personnel will be used to blind

supplies. Trial treatment identity (name, strength or potency) is included in the label text; random code/disclosure envelopes or lists are not provided.

9.4 Storage and Handling Requirements

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

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

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

9.5 Discard/Destruction/Returns and Reconciliation

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

9.6 Standard Policies

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

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

10.1 Confidentiality

10.1.1 Confidentiality of Data

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

10.1.2 Confidentiality of Subject Records

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

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

10.1.3 Confidentiality of Investigator Information

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

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

2. hospital or clinic address and telephone number;

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

4. other professional documentation.

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

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

10.1.4 Confidentiality of IRB/IEC Information

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

10.2 Compliance with Financial Disclosure Requirements

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

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

10.3 Compliance with Law, Audit and Debarment

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

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

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

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

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

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

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

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

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

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

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

According to European legislation, a Sponsor must designate an overall coordinating investigator for a multi-center trial (including multinational). When more than one trial site

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

10.4 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Amendments Act (FDAAA) of 2007 and the European Medicines Agency (EMA) clinical trial Directive 2001/20/EC, the Sponsor of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to http://www.clinicaltrials.gov, www.clinicaltrialsregister.eu or other local registries. Merck, as Sponsor of this trial, will review this protocol and submit the information necessary to fulfill these requirements. Merck entries are not limited to FDAAA or the EMA clinical trial directive mandated trials. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

By signing this protocol, the investigator acknowledges that the statutory obligations under FDAAA, the EMA clinical trials directive or other locally mandated registries are that of the Sponsor and agrees not to submit any information about this trial or its results to those registries.

10.5 Quality Management System

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

10.6 Data Management

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

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

10.7 Publications

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

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

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

paper may be of value. Limitations of single trial site observations in a multicenter trial should always be described in such a manuscript.

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

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

11.0 LIST OF REFERENCES

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

[2] Dong H, Strome SE, Salomao DR, Tamura H, Hirano F, Flies DB, et al. Tumor-associated B7-H1 promotes T-cell apoptosis: a potential mechanism of immune evasion. Nat Med 2002;8(8):793-800.

[3] Sharpe AH, Freeman GJ. The B7-CD28 superfamily. Nat Rev Immunol 2002;2(2):116-26.

[4] Brown JA, Dorfman DM, Ma F-R, Sullivan EL, Munoz O, Wood CR, et al. Blockade of programmed death-1 ligands on dendritic cells enhances T cell activation and cytokine production. J Immunol 2003;170(3):1257-66.

[5] Francisco LM, Sage PT, Sharpe AH. The PD-1 pathway in tolerance and autoimmunity. Immunol Rev 2010;236:219-42.

[6] Thompson RH, Dong H, Lohse CM, Leibovich BC, Blute ML, Cheville JC, et al. PD-1 is expressed by tumor-infiltrating immune cells and is associated with poor outcome for patients with renal cell carcinoma. Clin Cancer Res 2007;13(6):1757-61.

[7] Hino R, Kabashima K, Kato Y, Yagi H, Nakamura M, Honjo T, et al. Tumor cell expression of programmed cell death-1 ligand 1 is a prognostic factor for malignant melanoma. Cancer 2010;116:1757-66.

[8] Nomi T, Sho M, Akahori T, Hamada K, Kubo A, Kanehiro H, et al. Clinical significance and therapeutic potential of the programmed death-1 ligand/programmed death-1 pathway in human pancreatic cancer. Clin Cancer Res 2007;13(7):2151-7.

[9] Gao Q, Wang X-Y, Qiu S-J, Yamato I, Sho M, Nakajima Y, et al. Overexpression of PD-L1 significantly associates with tumor aggressiveness and postoperative recurrence in human hepatocellular carcinoma. Clin Cancer Res 2009;15(3):971-9.

[10] Hamanishi J, Mandai M, Iwasaki M, Okazaki T, Tanaka Y, Yamaguchi K, et al. Programmed cell death 1 ligand 1 and tumor-infiltrating CD8+ T lymphocytes are prognostic factors of human ovarian cancer. Proc Natl Acad Sci U S A 2007;104(9):3360-5.

[11] Fourcade J, Kudela P, Sun Z, Shen H, Land SR, Lenzner D, et al. PD-1 is a regulator of NY-ESO-1-specific CD8+ T cell expansion in melanoma patients. J Immunol 2009;182:5240-9.

[12] Cai G, Karni A, Oliveira EML, Weiner HL, Hafler DA, Freeman GJ. PD-1 ligands, negative regulators for activation of naïve, memory, and recently activated human CD4+ T cells. Cell Immunol 2004;230(2):89-98.

[13] Blank C, Mackensen A. Contribution of the PD-L1/PD-1 pathway to T-cell exhaustion: an update on implications for chronic infections and tumor evasion. Cancer Immunol Immunother. 2007 May;56(5):739-45.

[14] Iwai Y, Ishida M, Tanaka Y, Okazaki T, Honjo T, Minato N. Involvement of PD-L1 on tumor cells in the escape from host immune system and tumor immunotherapy by PD-L1 blockade. Proc Natl Acad Sci U S A 2002;99(19):12293-7.

[15] Tsushima F, Tanaka K, Otsuki N, Youngnak P, Iwai H, Omura K, et al. Predominant expression of B7-H1 and its immunoregulatory roles in oral squamous cell carcinoma. Oral Oncol 2006;42:268-74.

[16] Korman A, Chen B, Wang C, Wu L, Cardarelli P, Selby M. Activity of anti-PD-1 in murine tumor models: role of "host" PD-L1 and synergistic effect of anti-PD-1 and anti-CTLA-4 [Abstract]. J Immunol 2007;178:48.37.

[17] Oble DA, Loewe R, Yu P, Mihm MC Jr. Focus on TILs: prognostic significance of tumor infiltrating lymphocytes in human melanoma. Cancer Immun. 2009 Apr 2;9:3.

[18] Topalian SL, Hodi FS, Brahmer JR, Gettinger SN, Smith DC, McDermott DF, et al. Safety, activity, and immune correlates of Anti-PD-1 antibody in cancer. N Engl J Med. "in press" 2012.

[19] Patnaik A, Kang SP, Tolcher AW, Rasco DW, Papadopoulos KP, Beeram M, et al. 2012 ASCO Annual Meeting: Phase I study of MK-3475 (anti-PD-1 monoclonal antibody) in patients with advanced solid tumors.

[20] Hodi FS, O'Day SJ, McDermott DF, Weber RW, Sosman JA, Haanen JB, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med 2010;363(8):711-23.

[21] Chapman PB, Hauschild A, Robert C, Hannen JB, Ascierto P, Larkin J, et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. N Engl J Med 2011;364(26):2507-16.

[22] Robert C, Thomas L, Bondarenko I, O'Day S, Weber J, Garbe C, et al. Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. N Engl J Med 2011;364(26):2517-26.

[23] Bellati F, Visconti V, Napoletano C, Antonilli M, Frati L, Benedetti Panici P, et al. Immunology of gynecologic neoplasms: analysis of the prognostic significance of the immune status. Curr Cancer Drug Targets 2009;9(4):541-65.

[24] Ruffell B, DeNardo DG, Affara NI, Coussens LM. Lymphocytes in cancer development: polarization towards pro-tumor immunity. Cytokine Growth Factor Rev 2010;21:3-10.

[25] Shirabe K, Motomura T, Muto J, Toshima T, Matono R, Mano Y, et al. Tumor-infiltrating lymphocytes and hepatocellular carcinoma: pathology and clinical management. Int J Clin Oncol 2010;15:552-8.

[26] Al-Shibli K, Al-Saad S, Andersen S, Donnem T, Bremnes RM, Busund L-T. The prognistic value of intraepithelial and stromal CD3-, CD117- and CD138-positive cells in non-small cell lung carcinoma. APMIS 2010;118:371-82.

[27] Clark CE, Beatty GL, Vonderheide RH. Immunosurveillance of pancreatic adenocarcinoma: insights from genetically engineered mouse models of cancer. Cancer Lett 2009;279:1-7.

[28] Diederichsen ACP, Hjelmborg JvB, Christensen PB, Zeuthen J, Fenger C. Prognostic value of the CD4+/CD8+ ratio of tumour infiltrating lymphocytes in colorectal cancer and HLA-DR expression on tumour cells. Cancer Immunol Immunother 2003;52:423-8.

[29] Gao Q, Qiu S-J, Fan J, Zhou J, Wang X-Y, Xiao Y-S, et al. Intratumoral balance of regulatory and cytotoxic T cells is associated with prognosis of hepatocellular carcinoma after resection. J Clin Oncol 2007;25(18):2586-93.

[30] Hillen F, Baeten CIM, van de Winkel A, Creytens D, van der Schaft DWJ, Winnepenninckx V, et al. Leukocyte infiltration and tumor cell plasticity are parameters of aggressiveness in primary cutaneous melanoma. Cancer Immunol Immunother 2008;57(1):97-106.

[31] Laghi L, Bianchi P, Miranda E, Balladore E, Pacetti V, Grizzi F, et al. CD3+ cells at the invasive margin of deeply invading (pT3-T4) colorectal cancer and risk of post-surgical metastatsis: a longitudinal study. Lancet Oncol 2009;10:877-84.

[32] Li JF, Chu YW, Wang GM, Zhu TY, Rong RM, Hou J, et al. The prognostic value of peritumoral regulatory T cells and its correlation with intratumoral cyclooxygenase-2 expression in clear cell renal cell carcinoma. BJU Intern 2008;103:399-405.

[33] Nemolato S, Fanni D, Naccarato AG, Ravarino A, Bevilacqua G, Faa G. Lymphoepithelioma-like hepatocellular carcinoma: a case report and a review of the literature. World J Gastroenterol 2008;14(29):4694-6.

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

[35] Oshikiri T, Miyamoto M, Shichinohe T, Suzuoki M, Hiraoka K, Nakakubo Y, et al. Prognostic value of intratumoral CD8+ T lymphocyte in extrahepatic bile duct carcinoma as essential immune response. J Surg Oncol 2003;84:224-8.

[36] Piersma SJ, Welters MJP, van der Burg SH. Tumor-specific regulatory T cells in cancer patients. Human Immunol 2008;69:241-9.

[37] Rao UNM, Lee SJ, Luo W, Mihm Jr. MC, Kirkwood JM. Presence of tumor-infiltrating lymphocytes and a dominant nodule within primary melanoma are prognostic factors for relapse-free survival of patients with thick (T4) primary melanoma: pathologic analysis of the E1690 and E1694 intergroup trials. Am J Clin Pathol 2010;133:646-53.

[38] Sasaki A, Tanaka F, Mimori K, Inoue H, Kai S, Shibata K, et al. Prognostic value of tumor-infiltrating FOXP3+ regulatory T cells in patients with hepatocellular carcinoma. EJSO 2008;34:173-9.

[39] Shen Z, Zhou S, Wang Y, Li R, Zhong C, Liang C, et al. Higher intratumoral infiltrated Foxp3+ Treg numbers and Foxp3+/CD8+ ratio are associated with adverse prognosis in resectable gastric cancer. J Cancer Res Clin Oncol 2010;136:1585-95.

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

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

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

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

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

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

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

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

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

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

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

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

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

[53] Sierocki JS, Hilaris BS, Hopfan S, Martini N, Barton D, Golbey RB, et al. cis-Dichlorodiammineplatinum(II) and VP-16-213: an active induction regimen for small cell carcinoma of the lung. Cancer Treat Rep. 1979 Sep-Oct;63(9-10):1593-7.

[54] Fukuoka M, Furuse K, Saijo N, Nishiwaki Y, Ikegami H, Tamura T, et al. Randomized trial of cyclophosphamide, doxorubicin, and vincristine versus cisplatin and etoposide versus alternation of these regimens in small-cell lung cancer. J Natl Cancer Inst. 1991 Jun 19;83(12):855-61.

[55] Roth BJ, Johnson DH, Einhorn LH, Schacter LP, Cherng NC, Cohen HJ, et al. Randomized study of cyclophosphamide, doxorubicin, and vincristine versus etoposide and cisplatin versus alternation of these two regimens in extensive small-cell lung cancer: a phase III trial of the Southeastern Cancer Study Group. J Clin Oncol. 1992 Feb;10(2):282-91.

[56] Sundstrom S, Bremnes RM, Kaasa S, Aasebo U, Hatlevoll R, Dahle R, et al. Cisplatin and etoposide regimen is superior to cyclophosphamide, epirubicin, and vincristine regimen in small-cell lung cancer: results from a randomized phase III trial with 5 years' follow-up. J Clin Oncol. 2002 Dec 15;20(24):4665-72.

[57] Chute JP, Venzon DJ, Hankins L, Okunieff P, Frame JN, Ihde DC, et al. Outcome of patients with small-cell lung cancer during 20 years of clinical research at the US National Cancer Institute. Mayo Clin Proc. 1997 Oct;72(10):901-12.

[58] Mascaux C, Paesmans M, Berghmans T, Branle F, Lafitte JJ, Lemaitre F, et al. A systematic review of the role of etoposide and cisplatin in the chemotherapy of small cell lung cancer with methodology assessment and meta-analysis. Lung Cancer. 2000 Oct;30(1):23-36.

[59] Pujol JL, Carestia L, Daures JP. Is there a case for cisplatin in the treatment of small-cell lung cancer? A meta-analysis of randomized trials of a cisplatin-containing regimen versus a regimen without this alkylating agent. Br J Cancer. 2000 Jul;83(1):8-15.

[60] Hanna N, Bunn PA, Jr., Langer C, Einhorn L, Guthrie T, Jr., et al. Randomized phase III trial comparing irinotecan/cisplatin with etoposide/cisplatin in patients with previously untreated extensive-stage disease small-cell lung cancer. J Clin Oncol 2006;24(13):2038-43.

[61] Lara PN Jr, Natale R, Crowley J, Lenz HJ, Redman MW, Carleton JE, et al. Phase III trial of irinotecan/cisplatin compared with etoposide/cisplatin in extensive-stage small-cell lung cancer: clinical and pharmacogenomic results from SWOG S0124. J Clin Oncol. 2009 May 20;27(15):2530-5.

[62] Horn L, Mansfield AS, Szczesna A, Havel L, Krzakowski M, Hochmair MJ, et al. First-line atezolizumab plus chemotherapy in extensive-stage small-cell lung cancer. N Engl J Med. In press 2018.

[63] Reck M, Luft A, Szczesna A, Havel L, Kim SW, Akerley W, et al. Phase III Randomized Trial of Ipilimumab Plus Etoposide and Platinum Versus Placebo Plus Etoposide and Platinum in Extensive-Stage Small-Cell Lung Cancer. J Clin Oncol. 2016 Nov 25;34:3740-8.

[64] Skarlos DV, Samantas E, Kosmidis P, Fountzilas G, Angelidou M, Palamidas P, et al. Randomized comparison of etoposide-cisplatin vs. etoposide-carboplatin and irradiation in small-cell lung cancer. A Hellenic Co-operative Oncology Group study. Ann Oncol. 1994 Sep;5(7):601-7.

[65] Rossi A, Di Maio M, Chiodini P, Rudd RM, Okamoto H, Skarlos DV, et al. Carboplatin- or cisplatin-based chemotherapy in first-line treatment of small-cell lung cancer: the COCIS meta-analysis of individual patient data. J Clin Oncol. 2012 May 10;30(14):1692-8.

[66] Spiro SG, Souhami RL, Geddes DM, Ash CM, Quinn H, Harper PG, et al. Duration of chemotherapy in small cell lung cancer: a Cancer Research Campaign trial. Br J Cancer. 1989 Apr;59(4):578-83.

[67] Giaccone G, Dalesio O, McVie GJ, Kirkpatrick A, Postmus PE, Burghouts JT, et al. Maintenance chemotherapy in small-cell lung cancer: long-term results of a randomized trial. J Clin Oncol. 1993 Jul;11(7):1230-40.

[68] Hanna NH, Sandier AB, Loehrer PJ Sr, Ansari R, Jung SH, Lane K, et al. Maintenance daily oral etoposide versus no further therapy following induction chemotherapy with etoposide plus ifosfamide plus cisplatin in extensive small-cell lung cancer: a Hoosier Oncology Group randomized study. Ann Oncol. 2002 Jan;13(1):95-102.

[69] Ready NE, Pang HH, Gu L, Otterson GA, Thomas SP, Miller AA, et al. Chemotherapy With or Without Maintenance Sunitinib for Untreated Extensive-Stage Small-Cell Lung Cancer: A Randomized, Double-Blind, Placebo-Controlled Phase II Study-CALGB 30504 (Alliance). J Clin Oncol. 2015 May 20;33(15):1660-5.

[70] Beith JM, Clarke SJ, Woods RL, Bell DR, Levi JA. Long-term follow-up of a randomised trial of combined chemoradiotherapy induction treatment, with and without maintenance chemotherapy in patients with small cell carcinoma of the lung. Eur J Cancer. 1996 Mar;32A(3):438-43.

[71] Schiller JH, Adak S, Cella D, DeVore III RF, Johnson DH. Topotecan versus observation after cisplatin plus etoposide in extensive-stage small-cell lung cancer: E7593 - A phase III trial of the Eastern Cooperative Oncology Group. J Clin Oncol 2001;19(8):2114-22.

[72] National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology- Non-Small Cell Lung Cancer: version 2.2017 [Internet]. Fort Washington, PA: National Comprehensive Cancer Network (NCCN); 2016. Available from: https://www.nccn.org/professionals/physician_gls/f_guidelines.asp

[73] Fruh M, De Ruysscher D, Popat S, Crino L, Peters S, Felip E, et al. Small-cell lung cancer (SCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2013 Oct;24 Suppl 6:vi99-105.

[74] Rudin CM, Ismaila N, Hann CL, Malhotra N, Movsas B, Norris K, et al. Treatment of Small-Cell Lung Cancer: American Society of Clinical Oncology Endorsement of the American College of Chest Physicians Guideline. J Clin Oncol. 2015 Dec 1;33(34):4106-11.

[75] Seute T, Leffers P, ten Velde GP, Twijnstra A. Neurologic disorders in 432 consecutive patients with small cell lung carcinoma. Cancer. 2004 Feb 15;100(4):801-6.

[76] Komaki R, Cox JD, Whitson W. Risk of brain metastasis from small cell carcinoma of the lung related to length of survival and prophylactic irradiation. Cancer Treat Rep. 1981 Sep-Oct;65(9-10):811-4.

[77] Nugent JL, Bunn PA Jr, Matthews MJ, Ihde DC, Cohen MH, Gazdar A, et al. CNS metastases in small cell bronchogenic carcinoma: increasing frequency and changing pattern with lengthening survival. Cancer. 1979 Nov;44(5):1885-93.

[78] Hirsch FR, Paulson OB, Hansen HH, Vraa-Jensen J. Intracranial metastases in small cell carcinoma of the lung: correlation of clinical and autopsy findings. Cancer. 1982 Dec 1;50(11):2433-7.

[79] Auperin A, Arriagada R, Pignon JP, Le Pechoux C, Gregor A, Stephens RJ, et al. Prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission. Prophylactic Cranial Irradiation Overview Collaborative Group. N Engl J Med. 1999 Aug 12;341(7):476-84.

[80] Slotman B, Faivre-Finn C, Kramer G, Rankin E, Snee M, Hatton M, et al. Prophylactic cranial irradiation in extensive small-cell lung cancer. N Engl J Med. 2007 Aug 16;357(7):664-72.

[81] Le Pechoux C, Dunant A, Senan S, Wolfson A, Quoix E, Faivre-Finn C, et al. Standard-dose versus higher-dose prophylactic cranial irradiation (PCI) in patients with limited-stage small-cell lung cancer in complete remission after chemotherapy and thoracic radiotherapy (PCI 99-01, EORTC 22003-08004, RTOG 0212, and IFCT 99-01): a randomised clinical trial. Lancet Oncol. 2009 May;10(5):467-74.

[82] Johnson BE, Becker B, Goff WB 2nd, Petronas N, Krehbiel MA, Makuch RW, et al. Neurologic, neuropsychologic, and computed cranial tomography scan abnormalities in 2- to 10-year survivors of small-cell lung cancer. J Clin Oncol. 1985 Dec;3(12):1659-67.

[83] Fleck JF, Einhorn LH, Lauer RC, Schultz SM, Miller ME. Is prophylactic cranial irradiation indicated in small-cell lung cancer? J Clin Oncol. 1990 Feb;8(2):209-14.

[84] Varghese AM, Zakowski MF, Yu HA, Won HH, Riely GJ, Krug LM, et al. Small-cell lung cancers in patients who never smoked cigarettes. J Thorac Oncol. 2014 Jun;9(6):892-6.

[85] Ou SH, Ziogas A, Zell JA. Prognostic factors for survival in extensive stage small cell lung cancer (ED-SCLC): the importance of smoking history, socioeconomic and marital statuses, and ethnicity. J Thorac Oncol. 2009 Jan;4(1):37-43.

[86] American Cancer Society. Cancer facts and figures 2014 [Internet]. Atlanta: American Cancer Society; 2014. Available from: http://www.cancer.org/acs/groups/content/@research/documents/webcontent/acspc-042151.pdf.

[87] Gaspar LE, McNamara EJ, Gay EG, Putnam JB, Crawford J, Herbst RS, et al. Small-cell lung cancer: prognostic factors and changing treatment over 15 years. Clin Lung Cancer. 2012 Mar;13(2):115-22.

[88] Pietanza MC, Krug LM, Wu AJ, Kris MG, et al. Small Cell and Neuroendocrine Tumors of the Lung. In Devita, Hellman & Rosenberg, ed. Cancer: Principles and practice of Oncology. 10th ed. Philadelphia (PA): Lippincott, Williams & Wilkins; 2015. p. 536-559.

[89] Simon GR, Turrisi A. Management of small cell lung cancer: ACCP evidence-based clinical practice guidelines (2nd edition). Chest. 2007 Sep;132(3 Suppl):324S-339S.

[90] von Pawel J, Schiller JH, Shepherd FA, Fields SZ, Kleisbauer JP, Chrysson NG, et al. Topotecan versus cyclophosphamide, doxorubicin, and vincristine for the treatment of recurrent small-cell lung cancer. J Clin Oncol. 1999 Feb;17(2):658-67.

[91] O'Brien ME, Ciuleanu TE, Tsekov H, Shparyk Y, Cucevia B, Juhasz G, et al. Phase III trial comparing supportive care alone with supportive care with oral topotecan in patients with relapsed small-cell lung cancer. J Clin Oncol. 2006 Dec 1;24(34):5441-7.

[92] Eckardt JR, von Pawel J, Pujol JL, Papai Z, Quoix E, Ardizzoni A, et al. Phase III study of oral compared with intravenous topotecan as second-line therapy in small-cell lung cancer. J Clin Oncol. 2007 May 20;25(15):2086-92. Erratum in: J Clin Oncol. 2007 Aug 1;25(22):3387.

[93] Graus F, Dalmou J, Rene R, Tora M, Malats N, Verschuuren JJ, et al. Anti-Hu antibodies in patients with small-cell lung cancer: association with complete response to therapy and improved survival. J Clin Oncol. 1997 Aug;15(8):2866-72.

[94] Tanio Y, Watanabe M, Osaki T, Tachibana I, Kawase I, Kuritani T, et al. High sensitivity to peripheral blood lymphocytes and low HLA-class I antigen expression of small cell lung cancer cell lines with diverse chemo-radiosensitivity. Jpn J Cancer Res. 1992 Jul;83(7):736-45.

[95] Yazawa T, Kamma H, Fujiwara M, Matsui M, Horiguchi H, Satoh H, et al. Lack of class II transactivator causes severe deficiency of HLA-DR expression in small cell lung cancer. J Pathol. 1999 Jan;187(2):191-9.

[96] Koyama K, Kagamu H, Miura S, Hiura T, Miyabayashi T, Itoh R, et al. Reciprocal CD4+ T-cell balance of effector CD62Llow CD4+ and CD62LhighCD25+ CD4+ regulatory T cells in small cell lung cancer reflects disease stage. Clin Cancer Res. 2008 Nov 1;14(21):6770-9.

[97] Schultheis AM, Scheel AH, Ozretic L, George J, Thomas RK, Hagemann T, et al. PD-L1 expression in small cell neuroendocrine carcinomas. Eur J Cancer. 2015 Feb;51(3):421-6.

[98] Komiya T, Madan R. PD-L1 expression in small cell lung cancer. Eur J Cancer. 2015 Sep;51(13):1853-5.

[99] Ishii H, Azuma K, Kawahara A, Yamada K, Imamura Y, Tokito T, et al. Significance of programmed cell death-ligand 1 expression and its association with survival in patients with small cell lung cancer. J Thorac Oncol. 2015 Mar;10(3):426-30.

[100] Miao L, Lu Y, Xu Y, Zhang G, Huang Z, Gong L, et al. PD-L1 and c-MET expression and survival in patients with small cell lung cancer. Oncotarget. Forthcoming 2016.

[101] Berghoff AS, Ricken G, Wilhelm D, Rajky O, Widhalm G, Dieckmann K, et al. Tumor infiltrating lymphocytes and PD-L1 expression in brain metastases of small cell lung cancer (SCLC). J Neurooncol. 2016 Oct;130(1):19-29.

[102] Rizvi NA, Hellmann MD, Snyder A, Kvistborg P, Makarov V, Havel JJ, et al. Cancer immunology. Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer. Science. 2015 Apr 3;348(6230):124-8.

[103] Ott PA, Felip E, Hiret S, Kim DW, Morosky A, Saraf S, et al. Pembrolizumab in Patients With Extensive-Stage Small Cell Lung Cancer: Updated Survival Results From KEYNOTE-028. Poster session presented at: IASLC 17th World Conference on Lung Cancer; 2016 Dec 4-7; Vienna, AUT.

[104] Ardizzoni A, Hansen H, Dombernowsky P, Gamucci T, Kaplan S, Postmus P, et al. Topotecan, a new active drug in the second-line treatment of small-cell lung cancer: a phase II study in patients with refractory and sensitive disease. The European Organization for Research and Treatment of Cancer Early Clinical Studies Group and New Drug Development Office, and the Lung Cancer Cooperative Group. J Clin Oncol. 1997 May;15(5):2090-6.

[105] Depierre A, von Pawel J, Hans K, Moro D, Clark P, Gatzemeier U, et al. Evaluation of topotecan (Hycamtin) in relapsed small cell lung cancer (SCLC). A multicenter phase II study [abstract]. Lung Cancer. 1997; 18(1 Suppl):35. Abstract no. 126.

[106] Eckardt J, Gralla R, Palmer MC, Gandara D, Laplante J, Sandier A, et al. Topotecan (T) as Second-Line Therapy In Patients (Pts) with Small Cell Lung Cancer (SCLC): A Phase II Study [abstract]. Ann Oncol. 1996;7 Suppl 5:107. Abstract no. 513P.

[107] Eckardt J, Depierre A, Ardizzoni A, Von Pawel J, Fields S. Pooled analysis of topotecan (T) in the second-line treatment of patients (pts) with sensitive small cell lung cancer (SCLC). Proc Am Soc Clin Oncol. 1997;16. Abstract no. 1624.

[108] Langer CJ, Gadgeel SM, Borghaei H, Papadimitrakopoulou VA, Patnaik A, Powell SF, et al. Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: a randomised, phase 2 cohort of the open-label KEYNOTE-021 study. Lancet Oncol. 2016 Oct 9. [Epub ahead of print].

[109] Foster NR, Renfro LA, Schild SE, Redman MW, Wang XF, Dahlberg SE, et al. Multitrial evaluation of progression-free survival as a surrogate end point for overall survival in first-line extensive stage small-cell lung cancer. J Thorac Oncol. 2015 Jul;10(7):1099-106.

[110] Nishino M, Giobbie-Hurder A, Gargano M, Suda M, Ramaiya NH, Hodi FS. Developing a common language for tumor response to immunotherapy: immune-related response criteria using unidimensional measurements. Clin Cancer Res. 2013 Jul 15;19(14):3936-43.

[111] Garon EB, Rizvi NA, Hui R, Leighl N, Balmanoukian AS, Eder JP, et al. Pembrolizumab for the Treatment of Non-Small-Cell Lung Cancer. N Engl J Med. 2015 Apr 19.

[112] Smith TJ, Bohlke K, Lyman GH, Carson KR, Crawford J, Cross SJ, et al. Recommendations for the Use of WBC Growth Factors: American Society of Clinical Oncology Clinical Practice Guideline Update. J Clin Oncol. 2015 Oct 1;33(28):3199-212.

[113] Gralla RJ, Roila F, Tonato M, Herrstedt J. MASCC/ESMO Antiemetic Guideline 2013: Multinational association of supportive care in cancer.

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

[115] Robins JM, Tsiatis AA. Correcting for non-compliance in randomized trials using rank preserving structural failure time models. Commun Stat-Theor M 1991;20(8):2609-31.

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

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 response.2

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

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research

The specimens consented and/or collected in this trial as outlined in Section 7.1.3.4 will be used in various experiments to understand:

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

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

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

3. Summary of Procedures for Future Biomedical Research

a. Subjects for Enrollment

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

trial flow chart. If delayed, present consent at next possible Subject Visit. Consent forms signed by the subject will be kept at the clinical trial site under secure storage for regulatory reasons.

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

c. eCRF Documentation for Future Biomedical Research Specimens

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

d. Future Biomedical Research Specimen(s)

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

4. Confidential Subject Information for Future Biomedical Research

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

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

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

5. Biorepository Specimen Usage

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

6. Withdrawal From Future Biomedical Research

Subjects may withdraw their consent for Future Biomedical Research and ask that their biospecimens not be used for Future Biomedical Research. Subjects may withdraw consent at any time by contacting the principal investigator for the main trial. If medical records for the main trial are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@merck.com). Subsequently, the subject's specimens will be flagged in the biorepository and restricted to main study use only. If specimens were collected from study participants specifically for Future Biomedical Research, these specimens will be removed from the biorepository and destroyed. Documentation will be sent to the investigator confirming withdrawal and/or destruction, if applicable. It is the responsibility of the investigator to inform the subject of completion of the withdrawal and/or destruction, if applicable. Any analyses in progress at the time of request for withdrawal/destruction or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research trial data and results. No new analyses would be generated after the request is received.

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

7. Retention of Specimens

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

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

8. Data Security

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

9. Reporting of Future Biomedical Research Data to Subjects

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

If important research findings are discovered, the Sponsor may publish results, present results in national meetings, and make results accessible on a public website in order to rapidly report this information to doctors and subjects. Subjects will not be identified by name in any published reports about this study or in any other scientific publication or presentation.

10. Future Biomedical Research Study Population

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

11. Risks Versus Benefits of Future Biomedical Research

For 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.

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

12. Questions

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

13. References

1. National Cancer Institute: http://www.cancer.gov/dictionary/?searchTxt=biomarker
2. International Conference on Harmonization: Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories - E15; http://www.ich.org/LOB/media/MEDIA3383.pdf
3. Industry Pharmacogenomics Working Group. Understanding the Intent, Scope and Public Health Benefits of Exploratory Biomarker Research: A Guide for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/
4. Industry Pharmacogenomics Working Group. Pharmacogenomics Informational Brochure for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/

12.3 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;5:649-655. The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.	

12.4 Common Terminology Criteria for Adverse Events Version 4.0

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

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

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

* As published in the European Journal of Cancer:

New response evaluation criteria in solid tumours: revised RECIST guideline (Version 1.1). Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D, Verweij J. New response evaluation criteria in solid tumors: Revised RECIST guideline (Version 1.1). Eur J Cancer. 2009 Jan;45(2):228-247.

12.6 List of Abbreviations

Abbreviation/Term	Definition
1L	first-line
2L	second-line
ADA	anti-drug antibodies
AE	adverse event
AEOSI	adverse event of special interest
ALT	alanine aminotransferase
ANC	Absolute neutrophil count
ASaT	All Subjects as Treated
AST	aspartate aminotransferase
AUC	area under the plasma drug concentration time curve
β-HCG	beta-human chorionic gonadotropin
BCG	Bacillus Calmette–Guérin
BICR	blinded independent central review
BSA	body surface area
CBC	complete blood count
CI	confidence interval
C_{max}	maximum concentration
CR	complete response
CrCl	creatinine clearance
CSF	colony-stimulating factors
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
DL	dose level
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DOR	duration of response
ECG	electrocardiogram
ECIs	events of clinical interest

Abbreviation/Term	Definition
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EMA	European Medicines Agency
EOC	Executive Oversight Committee
EORTC	European Organization for Research and Treatment of Cancer
EP	etoposide/platinum
EQ-5D-5L	European Quality of Life Five-dimension Five-level Scale Questionnaire
ERC	Ethics Review Committee
ES-SCLC	extensive stage small cell lung cancer
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FSH	follicle-stimulating hormone
FT4	free thyroxine
GCP	Good Clinical Practice
GFR	glomerular filtration rate
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HR	hazard ratio
IA1	first interim analysis
IA2	second interim analysis
IB	Investigator's Brochure
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (formerly International Conference on Harmonisation)
IEC	Independent Ethics Committee
Ig	immunoglobulin
IgC	immunoglobulin constant
IgG	immunoglobulin G
IgV	immunoglobulin variable
IHC	immunohistochemistry

Abbreviation/Term	Definition
INR	international normalized ratio
irAE	immune-related adverse event
IRB	Institutional Review Board
irRECIST	Immune-related Response Evaluation Criteria in Solid Tumors
IRT	interactive response technology
ITT	intention-to-treat
IV	intravenous
IVRS/IWRS	interactive voice response system/integrated web response system
LDH	lactate dehydrogenase
LS-SCLC	limited-stage small cell lung cancer
MRI	magnetic resonance imaging
MSD	Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
N/A	not applicable
NCI	National Cancer Institute
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
OTC	over-the-counter
PBPK	physiologically based pharmacokinetics
PCI	prophylactic cranial irradiation
PD	progressive disease
PD-1	programmed cell death protein-1
PD-L1	programmed cell death-ligand 1
PD-L2	programmed cell death-ligand 2
PFS	progression-free survival
PK	pharmacokinetic
PR	partial response
PRO	patient-reported outcome
PT	prothrombin time
Q2W	every 2 weeks
Q3W	every 3 weeks
QLQ-C30	Quality of Life Questionnaire Core 30

Abbreviation/Term	Definition
QLQ-LC13	Quality of Life Questionnaire and Lung Cancer Module 13
RBC	red blood cell
RECIST 1.1	Response Evaluation Criteria in Solid Tumors version 1.1
RNA	ribonucleic acid
SAE	serious adverse events
SAP	Statistical Analysis Plan
SCLC	small cell lung cancer
SD	stable disease
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SOC	standard of care
sSAP	supplemental statistical analysis plan
T1DM	Type 1 diabetes mellitus
T3	triiodothyronine
TB	Bacillum Tuberculosis
TIL	tumor-infiltrating lymphocyte
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
WBRT	whole brain radiation therapy

13.0 SIGNATURES

13.1 Sponsor's Representative

TYPED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	

13.2 Investigator

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

TYPED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	

Supplemental Statistical Analysis Plan (sSAP)

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1. INTRODUCTION

This supplemental SAP (sSAP) is a companion document to the protocol. In addition to the information presented in the protocol SAP which provides the principal features of confirmatory analyses for this trial, this supplemental SAP provides additional statistical analysis details/data derivations and documents modifications or additions to the analysis plan that are not "principal" in nature and result from information that was not available at the time of protocol finalization.

2. SUMMARY OF CHANGES

This sSAP was amended to update the timing of the final analysis to match the SAP of protocol amendment 09.

3. STATISTICAL ANALYSIS PLAN SUMMARY

Key elements of the statistical analysis plan are summarized below; the comprehensive plan is provided in Sections 3.2 through 3.11.

Study Design Overview	This is a Phase 3, randomized, multi-site, double-blind study of 1L pembrolizumab+Etoposide/Platinum (EP) versus saline placebo+EP in Extensive Stage Small Cell Lung Cancer ES-SCLC
Treatment Assignment	Approximately 430 subjects will be randomized in a 1:1 ratio to receive pembrolizumab+EP or saline placebo+EP. The stratification factors used for this study are a) cisplatin vs carboplatin, b) ECOG status (0 vs 1), and, c) LDH at baseline (≤ vs > ULN). This is a double-blind study.
Analysis Populations	Efficacy: Intention-to-Treat (ITT) Safety: All Subjects as Treated (ASaT)
Primary Endpoints	1) PFS per RECIST 1.1 assessed by BICR 2) Overall survival (OS)
Secondary Endpoints	3) ORR per RECIST 1.1 assessed by BICR 4) DOR per RECIST 1.1 assessed by BICR 5) AEs
Statistical Methods for Key Efficacy Analyses	The primary hypotheses will be evaluated by comparing 1L pembrolizumab+EP to 1L saline placebo+EP based on PFS per RECIST 1.1 (BICR) and OS in subjects with ES-SCLC using a stratified log-rank test. Hazard ratios (HRs) will be estimated using a stratified Cox regression model. Event rates over time will be estimated within each treatment group using the Kaplan-Meier method.
Statistical Methods for Key Safety Analyses	The analysis of safety results will follow a tiered approach. There are no Tier 1 safety parameters in this trial. All safety parameters are considered either Tier 2 or Tier 3. Tier 2 parameters will be assessed via point estimates with 95% CIs provided for between-group comparisons; only point estimates by treatment group are provided for Tier 3 safety parameters. The between-treatment difference will be analyzed using the Miettinen and Nurminen method.
Interim Analyses	Two interim analyses are planned in this study. Results will be reviewed by the external DMC. Details are provided in Section 3.6 – Interim Analyses. • Interim analysis 1

	○ Timing: To be performed approximately 18 months from study start, where study start is the date on which the first subject was randomized. ○ Purpose: Interim PFS and OS analyses to demonstrate superiority of pembrolizumab+EP over saline placebo+EP.
	• Interim analysis 2 ○ Timing: To be performed approximately 22 months from study start. ○ Purpose: Final PFS analysis and interim OS analysis to demonstrate superiority of pembrolizumab+EP over saline placebo+EP
	• Final analysis ○ Timing: To be performed after a minimum of 294 deaths are observed or approximately 31 months after first subject enrolled, whichever occurs later. ○ Purpose: Primary analysis of OS to demonstrate superiority of pembrolizumab+EP over saline placebo+EP.
Multiplicity	The family-wise type I error rate for this study is strongly controlled at 2.5% (one-sided) for the hypothesis testing of ORR, PFS and OS. The multiplicity strategy will follow the graphical approach of Maurer and Bretz as described in Section 3.7 – Multiplicity, with 0.6% and 1.9% alpha initially allocated to the PFS and OS hypotheses, respectively. Group sequential methods will be used to allocate alpha between the interim and final analyses for PFS and OS endpoints. Further details of the interim analysis strategy can be found in Section 3.6 – Interim Analyses.
Sample Size and Power	The planned sample size is approximately 430 subjects. The actual sample size is 453 subjects. For PFS, based on 387 events, the study has 95.6% power to detect a HR of 0.65 (pembrolizumab+EP vs saline placebo+EP) at α=0.6% (one-sided). For OS, based on a minimum of 294 events, the study has at least 94.4% power to detect a HR of 0.65 (pembrolizumab+EP vs saline placebo+EP) at α=1.9% (one-sided).

3.1 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 Sponsor will generate the randomized allocation schedule for study treatment assignment for this protocol and the randomization will be implemented in IVRS/IWRS.

Planned interim analyses are described in Section 3.6. Participant-level unblinding will be restricted to an external unblinded statistician and scientific programmer performing the interim analysis, who will have no other responsibilities associated with the study.

An external DMC will be convened to review accumulating safety data to provide an opportunity to terminate the study early if there are concerns regarding safety. Treatment-level results at the interim analyses will be provided by the external unblinded statistician to the DMC. The DMC will also review the unblinded efficacy results at the planned interim analyses. The DMC responsibilities and review schedules will be outlined in the DMC charter. The recommendation of the DMC will be communicated to the Sponsor EOC and, in the event of a recommendation to

halt the trial early due to safety concerns, to the appropriate regulatory agencies. If the DMC recommends modifications to the design of the protocol or discontinuation of the study, the EOC may be unblinded to results at the treatment level in order to act on these recommendations. Participant-level unblinding to support regulatory filing, should one occur before the end of the study, will be restricted to a designated Sponsor/MSD team, who will have no other responsibilities associated with the study.

The extent to which individuals are unblinded with respect to the results will be documented. Additional logistical details, revisions to the above plan, and data monitoring guidance will be provided in the DMC Charter.

3.2 HYPOTHESES/ESTIMATION

Objectives and hypotheses of the study are stated in Protocol Section Section 3.0 – Objective(s) and hypothesis(es).

3.3 ANALYSIS ENDPOINTS

Efficacy and safety endpoints that will be evaluated are listed below.

3.3.1 Efficacy Endpoints

Primary

Progression-free Survival – RECIST 1.1 assessed by BICR

Progression-free-survival is defined as the time from randomization to the first documented disease progression per RECIST 1.1 based on BICR or death due to any cause, whichever occurs first. See Section 3.5.1 – Statistical Methods for Efficacy Analyses for definition of censoring.

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 analysis will be censored at the date of last known contact.

Secondary

Objective Response Rate – RECIST 1.1 assessed by BICR

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

Duration of Response – RECIST 1.1 assessed by BICR

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

Exploratory

Exploratory endpoints of this study include:

1. ORR, DOR and PFS per immune-related RECIST (irRECIST) as assessed by the investigator.
2. ORR and PFS per RECIST 1.1 by BICR, and OS by PD-L1 expression (TPS <1% versus ≥1%, CPS <1 versus ≥1).

3.3.2 Safety Endpoints

Safety measurements are described in the protocol in Section 4.2.3.3 – Safety Endpoints and Section 7 – Trial Procedures. Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs, laboratory tests, and vital signs. Safety parameters to be analyzed include, but are not limited to, AEs, SAEs, fatal AEs, and laboratory changes. Furthermore, specific events will be collected and designated as ECIs as described in Section 7.2.3 – Immediate Reporting of Adverse Events in the protocol.

3.3.3 Patient Reported Outcome (PRO) Endpoints

Secondary

Mean change in Score

Mean change from baseline at Week 18 in the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) global health status/quality of life scores (Items 29-30). If the overall PRO completion or compliance rates at Week 18 are less than 60% or 80%, respectively, then the primary analysis time point will be moved to the next earliest time point in which the rates are at least 60% for completion and at least 80% for compliance.

Time-to-deterioration (TTD)

For the EORTC QLQ-C30 and QLQ-LC13, a 10 points or greater worsening from baseline for each scale represents a clinically relevant deterioration based on prior literature. Time-to-deterioration is defined as the time to first onset of 10 or more (out of 100) deterioration from baseline in a given scale/sub-scale/item and confirmed by a second adjacent 10 or more deterioration from baseline under a right-censoring rule. The endpoint of interest is the composite endpoint of cough (QLQ-LC-13 Item 1), chest pain (QLQ-LC-13 Item 10), or dyspnea (QLQ-C30 Item 8).

Exploratory

The PRO endpoints which will be used for exploratory analyses are:

- mean change in score from baseline at weeks 18 of Physical functioning scale (QLQ-C30 Items 1-5) and EQ-5D-5L Health State Score using visual analogue scale (VAS)
- time-to deterioration for Global Health Status/QoL scale (QLQ-C30 Items 29-30) and Physical functioning scale (QLQ-C30 Items 1-5)

- Proportion improved/stable in Global Health Status/QoL scale (QLQ-C30 Items 29-30) and Physical functioning scale (QLQ-C30 Items 1-5). Improved/Stable is defined as an improvement or less than 10 points worsening in score from baseline at any time during the trial and confirmed by improvement or less than 10 points worsening at the next consecutive visit.

3.4 ANALYSIS POPULATIONS

3.4.1 Efficacy Analysis Populations

The analyses 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 3.5 Statistical Methods.

3.4.2 Safety Analysis Populations

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

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

3.4.3 PRO Analysis Population

The primary analysis approach for the pre-specified PRO endpoints will be based on a quality of life related full analysis set (FAS) population following the intention-to-treat (ITT) principle and ICH E9 guidelines. This population consists of all randomized patients who have received at least one dose of study medication and have completed at least one PRO assessment.

3.5 STATISTICAL METHODS

This section describes the statistical methods that address the primary, secondary and exploratory objectives as stated in the protocol.

Statistical methods for efficacy analyses are described in Section 3.5.1. Statistical testing and inference for safety analyses are described in Section 3.5.2. Efficacy results that will be deemed to be statistically significant after consideration of the Type I error control strategy are described in Section 3.7, 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.

3.5.1 Statistical Methods for Efficacy Analyses

3.5.1.1 Progression-Free Survival (PFS)

The non-parametric Kaplan-Meier method will be used to estimate the PFS curve in each treatment group. The treatment difference in PFS will be assessed by the stratified log-rank test. A stratified Cox proportional hazard model with Efron's method of tie handling will be used to assess the magnitude of the treatment difference (ie, the HR) between the treatment arms. The HR and its 95% CI from the stratified Cox model with Efron's method of tie handling and with a single treatment covariate will be reported. The stratification factors used for randomization will be applied to both the stratified log-rank test and the stratified Cox model. In case there is a stratum which has =<10 subjects, the stratum will be combined with the stratum with the next smallest number of subjects till the number of subject in the smallest stratum is >10. The same strategy will be used for determining the strata for the stratified analyses of OS, ORR and PROs.

Since disease progression is assessed periodically, PD can occur any time in the time interval between the last assessment where PD was not documented and the assessment when PD is documented. For the primary analysis, for the subjects who have PD, the true date of disease progression will be approximated by the date of the first assessment at which PD is objectively documented per RECIST 1.1 (BICR), regardless of discontinuation of study drug. Death is always considered as a confirmed PD event. Sensitivity analyses will be performed for comparison of PFS based on investigator's assessment.

In order to evaluate the robustness of the PFS endpoint per RECIST 1.1 by central imaging vendor, we will perform 2 sensitivity analyses with a different set of censoring rules. The first sensitivity analysis is the same as the primary analysis except that it censors at the last disease assessment without PD when PD or death is documented after more than one missed disease assessment. The second sensitivity analysis is the same as the primary analysis except that it considers discontinuation of treatment or initiation of an anticancer treatment subsequent to discontinuation of study-specified treatments, whichever occurs later, to be a PD event for subjects without documented PD or death. The censoring rules for primary and sensitivity analyses are summarized in Table 1.

Table 1 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
No PD and no death; ≥ 2 consecutive missed disease assessments	Censored at last disease assessment	Censored at last disease assessment prior to ≥2 consecutive missed visits	Censored at last disease assessment
PD or death documented after ≤ 1 missed disease assessment	Progressed at date of documented PD or death	Progressed at date of documented PD or death	Progressed at date of documented PD or death
PD or death documented at any time after ≥ 2 missed disease assessments	Progressed at date of documented PD or death	Censored at last disease assessment prior to the ≥ 2 missed disease assessment	Progressed at date of documented PD or death

Restricted Mean Survival Time (RMST) method (Uno et al. [5]) may be conducted for PFS to account for the possible non-proportional hazards effect.

3.5.1.2 Overall Survival (OS)

The non-parametric Kaplan-Meier method will be used to estimate the survival curves. The treatment difference in survival will be assessed by the stratified log-rank test (based on the stratification factor defined in Section 5.4 of the Protocol– Stratification). A stratified Cox proportional hazard model with Efron's method of tie handling will be used to assess the magnitude of the treatment difference (ie, the HR). The HR and its 95% CI from the stratified Cox model with a single treatment covariate will be reported. The same stratification factors as used for PFS analysis in the overall population will be applied to both the stratified log-rank test and the stratified Cox model. Restricted Mean Survival Time (RMST) method may be conducted for OS to account for the possible non-proportional hazards effect.

Since subjects in the Placebo+EP arm are expected to discontinue from the study earlier compared to subjects in the pembrolizumab arm because of earlier onset of PD and may switch to another anti PD-1 treatment following confirmation of PD, adjustment for the effect of crossover on OS may be performed based on recognized methods, (eg, the Rank Preserving Structural Failure Time (RPSFT) model proposed by Robins and Tsiatis), based on an examination of the appropriateness of the data to the assumptions required by the method used.

3.5.1.3 Objective Response Rate (ORR)

Stratified Miettinen and Nurminen's method will be used for comparison of ORR between the treatment groups. The difference in ORR and its 95% CI from the stratified Miettinen and Nurminen method with strata weighting by sample size will be provided. The same stratification factors as used for PFS and OS analyses will be used as stratification factors in the analysis.

3.5.1.4 Duration of Response (DOR)

For subjects who demonstrate CR or PR, DOR is defined as the time from first documented evidence of CR or PR until disease progression or death due to any cause, whichever occurs first. Censoring rules for DOR are summarized in Table 2. DOR will be assessed using RECIST 1.1 by BICR.

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

Table 2 Censoring Rules for DOR

Situation	Date of Progression or Censoring	Outcome
No progression nor death, no new anti-cancer therapy initiated	Last adequate disease assessment	Censor (non-event)
No progression nor death, new anti-cancer therapy initiated	Last adequate disease assessment before new anti-cancer therapy initiated	Censor (non-event)
Death or progression after ≥2 consecutive missed disease assessments	Last adequate disease assessment prior to ≥2 missed adequate disease assessments	Censor (non-event)
Death or progression after ≤1 missed adequate disease assessments	Progressive disease or death	End of response (Event)
A missed disease assessment includes any assessment that is not obtained or is considered inadequate for evaluation of response.		

Table 3 summarizes the key efficacy analyses.

Table 3 Efficacy Analysis Methods for Primary and Secondary Efficacy Endpoints

Endpoint/Variable (Description, Time Point)	Statistical Method	Analysis Population	Missing Data Approach
Primary Analyses:			
PFS (RECIST 1.1) by BICR	Testing: Stratified Log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT	Censored according to rules in Table 1
OS	Testing: Stratified Log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT	Censored at last known alive date
Secondary Analyses:			
ORR (RECIST 1.1) by BICR	Stratified Miettinen and Nurminen method	ITT	Subjects with missing data are considered non-responders
DOR (RECIST 1.1) by BICR	Summary statistics using Kaplan-Meier method	All responders in ITT	Non-responders are excluded in analysis

The strategy to address multiplicity issues with regard to multiple treatment comparisons, multiple endpoints, multiple populations, and interim analyses is described in Section 3.6, Interim Analyses and in Section 3.7, Multiplicity.

3.5.2 Statistical Methods for Safety Analyses

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

The analysis of safety results will follow a tiered approach (Table 4). The tiers differ with respect to the analyses that will be performed. Safety parameters or AEs 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.

Adverse events of special interest (AEOSIs) that are immune-mediated or potentially immune-mediated are well documented and will be evaluated separately; however, these events have been characterized consistently throughout the pembrolizumab clinical development program and determination of statistical significance is not expected to add value to the safety evaluation. Further, pembrolizumab added to platinum doublets studied thus far have not been found to impact safety, and in an ongoing Phase 1 clinical trial, the chemotherapeutic regimen used here with pembrolizumab has not led to increased toxicity (NCT02402920). Additionally, there are no known AEs associated with subjects with SCLC for which determination of a p-value is expected

to impact the safety assessment. For these reasons, there are no events of interest that warrant inferential testing. Therefore, there are no Tier I events in this study.

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

The threshold of at least 10% was chosen for membership in Tier 2 because subjects enrolled in this study are in critical condition and usually experience various AEs of similar types regardless of treatment, events reported less frequently than in 10% of subjects would obscure the assessment of the overall safety profile and add little to the interpretation of potentially meaningful treatment differences. In addition, Grades 3 to 5 AEs (≥5% of subjects in one of the treatment arms) and SAEs (≥5% of subjects in one of the treatment arms) will be considered Tier 2 events. For Tier 2 events, 95% CIs will be provided for between-treatment differences in the percentage of subjects with events; these analyses will be performed using the Miettinen and Nurminen method , an unconditional, asymptotic method. Because many 95% CIs may be provided without adjustment for multiplicity, the CIs should be regarded as a helpful descriptive measure to be used in safety review, not a formal method for assessing the statistical significance of the between-treatment differences.

For laboratory parameters, the number and percentage of subjects with increases from baseline in laboratory test toxicity grades based on the highest post-baseline toxicity grade and shift of toxicity grade from baseline to the worst post-baseline toxicity grade will be summarized by treatment arm.

Table 4 Analysis Strategy for Safety Parameters

Safety Tier	**Safety Endpoint**	**95% CI for Treatment Comparison**	**Descriptive Statistics**
Tier 2	Any AE (≥10% of subjects in one of the treatment arms)	X	X
	Any Grades 3 to 5 AE (≥5% of subjects in one of the treatment arms)	X	X
	Any serious AE (≥5% of subjects in one of the treatment arms)	X	X
Tier 3	Any AE		X
	Any change from baseline results (laboratory tests)		X
Abbreviations: AE=adverse event, CI=confidence interval			

Exposure-Adjusted Approach

To properly account for the potential difference in follow-up time between the study arms, which is expected to be longer in the pembrolizumab arm, summary of AE incidence adjusted for treatment exposure analyses may be provided as appropriate.

3.5.3 Summaries of Baseline Characteristics and Demographics

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.

3.5.4 Patient Reported Outcomes (PRO) Analysis

This section describes the planned analyses for the key PRO endpoints. As there is no formal hypothesis testing for PRO endpoints, nominal p-values will be provided for treatment comparisons of pembrolizumab combination therapy vs. standard of care. No multiplicity adjustment will be performed.

PRO compliance summary

Completion and compliance of QLQ-C30, LC13 and EQ-5D-5L by visit and by treatment will be described within the PRO FAS population. Numbers and percentages of complete and missing data at each visit will be summarized for each of the treatment groups.

Completion Rate is defined as the percentage of observed visit over number of randomized subjects at each time points.

$$Completion\ Rate = \frac{Number\ of\ Subjects\ who\ Complete\ at\ least\ one\ Item}{Number\ of\ Randomized\ Subjects}$$

The completion rate is expected to shrink in the later visit during study period due to the subjects who discontinued early. Therefore, another measurement, Compliance Rate, defined as the percentage of observed visit over number of eligible subjects who are expected to complete the PRO assessment (not including the subjects missing by design (such as death, discontinuation, translation not available) will be employed as the support for completion rate).

$$Compliance\ Rate = \frac{Number\ of\ Subjects\ who\ Complete\ at\ least\ one\ Item}{Number\ of\ Eligible\ Subjects\ who\ are\ Expected\ to\ Complete}$$

The reasons of non-completion and non-compliance will be provided in supplementary table:

- Completed as scheduled
- Not completed as scheduled
- Off-study: not scheduled to be completed.

In addition, reasons for non-completion as scheduled of these measures will be collected using "miss_mode" forms filled by site personnel and will be summarized in table format. An instrument is considered complete as at least one valid score available according to the missing item rules outlined in the EORTC Manual.

The schedule for PRO data collection:

PROs were scheduled to be completed every cycle for Cycles 1 to 9 while the subject was receiving study treatment, then every other cycle up to Cycle 17 (ie, Cycles 11, 13, 15, and 17). PROs were also scheduled to be obtained at the Treatment Discontinuation visit and 30-day Safety Follow-up visit. For analysis purposes, relative visit days were mapped into analysis visits. The general rule of mapping relative day to analysis visit is provided in Table 5. Due to space restrictions visit windows until week 30 are provided.

Table 5 Mapping Relative Day to Analysis Visit

Treatment Week	Week									
	Baseline	3	6	9	12	15	18	21	24	30
Day	1	21	42	63	84	105	136	147	168	210
Range	[-7,7]	[8,31]	[32,52]	[53,73]	[74,94]	[95,115]	[116,136]	[137,157]	[158,188]	[189,230]

Analysis of Mean Score Change

To assess the treatment effects on the PRO, for each continuous endpoint defined, a constrained longitudinal data analysis (cLDA) method proposed by Liang and Zeger [1] will be used. This model assumes a common mean across treatment groups at baseline and a different mean for each treatment at each of the post-baseline time points. In this model, the response vector consists of baseline and the values observed at each post-baseline time point. Time is treated as a categorical variable so that no restriction is imposed on the trajectory of the means over time. The analysis model will include the PRO score as the response variable, with covariates including treatment by study visit interaction, and the same stratification factors as used in the stratified analyses of efficacy endpoints. The treatment difference in terms of mean PRO score change from baseline at week 18 (time defined by time windows instead of study visit) will be estimated and tested from this model. If the overall PRO completion or compliance rates at Week 18 are less than 60% or 80%, respectively, then the primary analysis time point will be moved to the next earliest time point in which the rates are at least 60% for completion and at least 80% for compliance.

An unstructured covariance matrix will be used to model the correlation among repeated measurements. The cLDA model is specified as follows:

$$E(Y_{ijt}) = \gamma_0 + \gamma_{jt} I(t > 0) + \beta X_i , \quad j = 1, 2 \quad t = 0,1,2,..k$$

where Y_{ijt} is the PRO score for subject i, with treatment assignment j, at visit t, γ_0 is the baseline mean for all treatment groups, γ_{jt} is the mean change from baseline for treatment group j at time t, X_i is the stratification factor (binary) vector for this patient, and β is the coefficient vector for stratification factors.

Based on the cLDA model, group-wise comparisons will be performed and the differences in the lsmean change from baseline will be reported, together with 95% C.I. and nominal p-value at the primary analysis time points. In addition, model-based lsmean score with 95% C.I. will be provided by treatment group and study visit.

The analysis of mean change will be based primarily under the assumption of missing-at-random (MAR) mechanism. The cLDA model implicitly treats missing data as missing at random (MAR).

Analyses of change from baseline to Week 18 will be displayed in tables for the following scales as listed in section 3.2.3: EORTC QLQ-C30 GHS/QoL (QLQ-C30 Items 29-30), Physical functioning scale (QLQ-C30 Items 1-5), and EQ-5D-5L VAS.

The empirical mean change (with 95% CIs) from baseline across time will be displayed graphically for the following scales: EORTC QLQ-C30 GHS/QoL (QLQ-C30 Items 29-30), Physical functioning scale (QLQ-C30 Items 1-5), and EQ-5D-5L VAS.

Analyses of LS mean change (95% CI) from baseline to Week 18 will be displayed in bar plot format for the following questionnaires in 3 separate figures: 1) EORTC QLQ-C30 global health status and functional status scales, 2) EORTC QLQ-C30 symptom scales, 3) EORTC QLQ-LC13 scales.

Time-to-Deterioration (TTD) Analysis

The TTD is defined as the time to first onset of 10 or more points deterioration from baseline with confirmation under right-censoring rule. The non-parametric Kaplan-Meier method will be used to estimate the deterioration curve in each treatment group. The estimate of median time to deterioration and its 95% confidence interval will be obtained from the Kaplan-Meier survival estimates. The treatment difference in TTD will be assessed by the stratified log-rank test. A stratified Cox proportional hazard model with Efron's method of tie handling and with a single treatment covariate will be used to assess the magnitude of the treatment difference (hazard ratio). The same stratification factors as used for efficacy endpoints will be used as stratification factors for both Cox model and log-rank test.

The primary approach for the time-to-deterioration analysis will be based on the assumption of non-informative censoring. The patients who do not have deterioration on the last date of evaluation will be censored. Table 6 provides censoring rule for TTD analysis.

Table 6 Censoring Rules for Time-to-Deterioration

Scenario	Outcome
No baseline assessments	Right censored at treatment start date
Deterioration documented	Event observed at time of assessment (first deterioration)
Ongoing or discontinued from study without deterioration	Right censored at time of last assessment

Analysis of Overall Improvement/Stability

Overall Improved/Stable rate will be calculated as the percentage of subjects who have improvement or less than 10 points worsening in score from baseline at any time during the trial and confirmed by an improvement or a less than 10 points worsening at the next consecutive visit. The stratified Miettinen and Nurminen method will be used for comparison of the overall improvement/stability rate between the treatment groups. The difference in overall improvement/stability rate and its 95% CI from the stratified Miettinen and Nurminen method with strata weighting by sample size will be provided. The same stratification factors as used for efficacy endpoints will be used for analysis.

3.6 INTERIM ANALYSES

Two interim efficacy analyses are planned for this study.

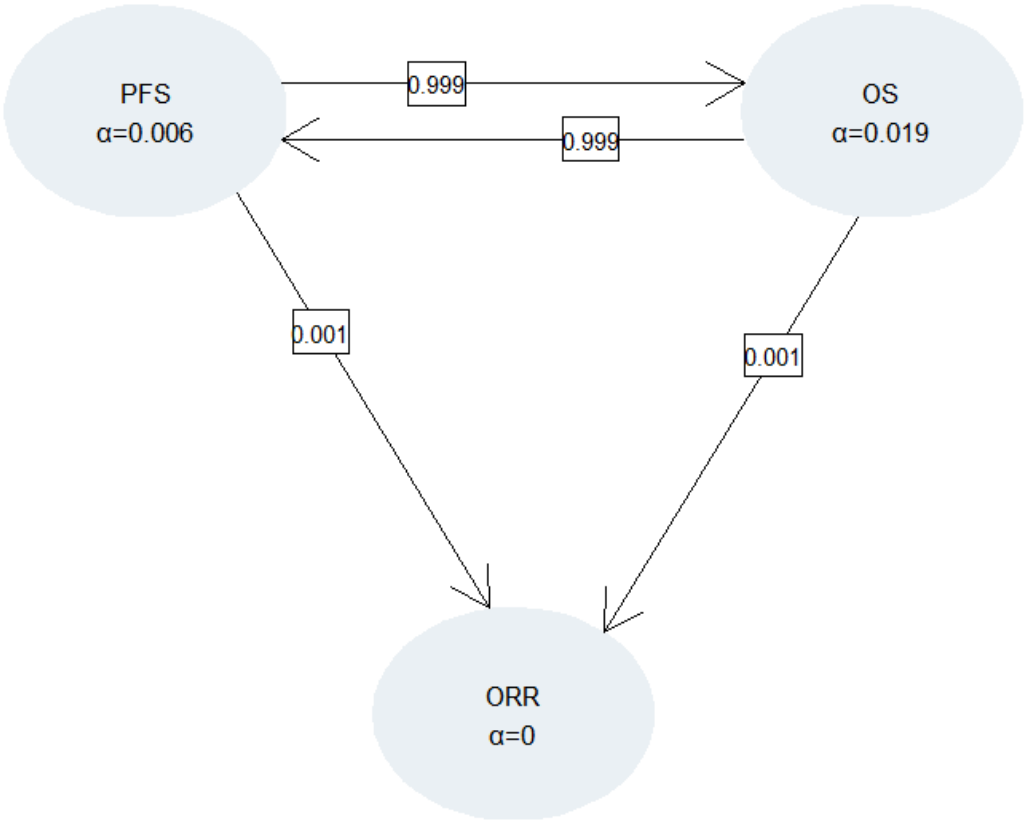
- The first interim analysis (IA1) will be performed approximately 18 months from study start, 3.5 months after the last patient was enrolled. PFS and OS will be evaluated at IA1. ORR p-value from IA1 may be evaluated for statistical significance if PFS and OS null hypotheses are rejected at IA1 or at a later analysis time.
- The second interim analysis (IA2) will be performed approximately 22 months from study start, 7.5 months after the last patient was enrolled. The second interim analysis evaluation of OS and the final evaluation of PFS will be performed at this time.
- The final analysis will evaluate OS only. It is planned when a minimum of 294 deaths have been observed or approximately 31 months after first subject enrolled, whichever occurs later.

In addition to the formal efficacy analyses, the DMC will conduct regular safety monitoring, the timing of which is specified in the DMC charter. Decisions to stop the trial early will be based on DMC recommendations with review by the EOC.

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

3.7 MULTIPLICITY

The trial uses the graphical method of Maurer and Bretz to control multiplicity for multiple hypotheses as well as interim analyses. Figure 1 shows the initial one-sided α allocation for each hypothesis in the ellipse representing the hypothesis. The weights for reallocation from each hypothesis to the others are represented in the boxes on the lines connecting hypotheses.



Note: If both PFS and OS null hypotheses are rejected, the reallocation strategy allows testing of ORR at alpha=0.025.

Figure 1 Multiplicity Graph for Type I Error Control

Progression-free Survival

If the null hypothesis for OS is rejected, shows that its α=0.019 is essentially fully reallocated to PFS hypothesis testing. Thus, the PFS null hypothesis Figure 1 may be tested at α=0.006 or at α=0.025. For PFS hypotheses, the targeted number of events at the final PFS analysis will be 387. A Lan-DeMets O'Brien-Fleming spending function will be used for information fraction-based alpha-spending to generate the group sequential design. The bounds provided in Table 7 are based on the assumption that the number of events at IA1 and IA2 are 332 and 387 respectively. The actual boundaries and the nominal alpha level will be determined based on the actual number of PFS events observed at the time of the analyses and from the overall alpha level after any potential alpha-shifting as the result of a successful OS analysis. The final PFS analysis at IA2 will use the remaining Type I error not spent at IA1, regardless of the actual number of PFS events observed. The p-value bound at the final PFS analysis will be calculated by considering the correlation between the test statistics as determined by the actual number of PFS events at IA1 and the final PFS analysis at IA2. The bounds given in Table 7 will be adjusted accordingly.

Table 7 Efficacy Boundaries and Properties for Progression-free Survival Analyses

Analysis	Targeted Analysis Time	Cumulative alpha spent[3]	Efficacy Bars[3]
IA1 (86%[2])	Around 18 months from study start[1]	0.003	• (One-sided) p-value <0.003 Observed HR <~0.74
IA2 (100%[2])	Around 22 months from study start[1]	0.006	• (One-sided) p-value <0.0051 Observed HR <~0.77

[1]Study start is defined as the date when the first subject was randomized.
[2]Percentage of expected number of events at final analysis targeted at interim analysis
[3]Nominal alpha, boundaries and cumulative alpha are based on the assumption that 332 and 387 events are at IA1 and IA2 respectively. The p-value boundaries will be updated at the time of analyses based on actual number of PFS events.

Note that if the α-reallocation from OS hypothesis testing occurs at the final analysis after hypothesis testing for PFS has been completed, the previously computed PFS test statistic for the PFS final analysis may be re-evaluated based on the updated bounds.

Overall Survival

The OS hypothesis may be tested at α=0.019 (initially allocated α) or at α=0.025 (if PFS null hypothesis is rejected) following the multiplicity strategy as outlined in Figure 1 bounds and boundary properties for OS hypothesis testing at the initial alpha level are demonstrated in Table 8 The alpha spending at each interim analysis is determined using a Lan-DeMets O'Brien-Fleming spending function, and the information fraction (ratio of the actual number of events at the interim analysis relative to a targeted 294 events at the final analysis). The final analysis will use the remaining Type I error not spent at earlier analyses, regardless of the number of events observed at the final analysis. The p-value bounds at second interim and final analysis will be calculated by considering the correlation between the test statistics as determined by the actual number of OS events at the previous and current analysis. The p-value bounds at each analysis time may also be updated after potential alpha-shifting as the result of a successful PFS analysis.

Table 8 Efficacy Boundaries and Properties for Overall Survival Analyses

Analysis	Targeted Analysis Time	Cumulative alpha spent[3]	Efficacy Bars[3]
IA1 (60%[2])	Approximately 18 months from study start[1]	0.0024	• (One-sided) p-value <0.0024 • Observed HR <~0.65
IA2 (76%[2])	Approximately 22 months from study start[1]	0.0071	• (One-sided) p-value <0.0064 • Observed HR <~0.72
FA (100%[2])	Approximately 294 deaths observed in two arms; approximately 31 months from study start	0.019	• (One-sided) p-value <0.0167 • Observed HR <~0.78

[1]Study start is defined as the date when the first subject was randomized.
[2]Percentage of expected number of events at final analysis targeted at interim analysis
[3] Nominal alpha, boundaries and cumulative alpha are based on the number of deaths expected assuming the projected number of events using protocol assumptions, i.e., 175, 224 and 294 at IA1, IA2 and final analysis respectively. The p-value boundaries will be updated at the time of analyses based on actual number of deaths.

The DMC has responsibility for assessment of overall risk: benefit. When prompted by safety concerns, the DMC can request corresponding efficacy data. DMC review of efficacy data to assess the overall risk: benefit to study participants will not require a multiplicity adjustment typically associated with a planned efficacy IA. However, if the DMC confirms that efficacy data were considered in the overall risk: benefit assessment during periodic safety reviews, a sensitivity analysis for OS taking a nominal alpha penalty of 0.000001 for each of such incidence will be conducted.

Objective Response Rate

The trial does not allocate initial alpha to ORR. ORR will be formally tested only if the hypotheses for PFS and OS are significant. The testing of ORR will be based on the first 352 subjects enrolled in the trial. If the null hypotheses for OS and PFS are rejected at IA1 or at a time later than IA1, the p-value of ORR from the IA1 analysis will be compared to an α-level of 0.025. Power at the possible α-level as well as the approximate treatment difference required to

reach the bound (ΔORR) are shown in Table 9 assuming underlying 50% and 70% response rates in the control and experimental groups, respectively.

Table 9 Possible Alpha-levels and Approximate ORR Difference Required to Demonstrate Efficacy for ORR

α	~ΔORR	Power
0.025	0.1002	0.9719

3.8 SAMPLE SIZE AND POWER CALCULATIONS

Four hundred and thirty subjects were planned to be randomized in 1:1 ratio into pembrolizumab+EP and the saline placebo+EP arms. By the time of the current amendment, 453 subjects were enrolled for this study.

The final PFS analysis for the study will occur about 22 months from study start. If 387 PFS events occur by the time of the final PFS analysis, the study will have a power of 96% approximately to demonstrate a hazard ratio of 0.65 on PFS at initially allocated α=0.006.

The final OS analysis will occur when at least 294 events have occurred or approximately 31 months from study start, whichever occurs later. With a minimum of 294 events at the time of final analysis, the study has at least 94% power to demonstrate a HR of 0.65 on OS at initially allocated α=0.019. The above power calculations for OS and PFS are based on the following assumptions: 1) 453 subjects were enrolled over 14.5 months following the actual enrollment pattern; 2) median PFS is 4.3 months in the control arm and hazard ratio is 0.65; 3) median OS is 10 months in the control arm and hazard ratio is 0.65; 4) The exponential dropout rates assumed for OS and PFS are 1% per month.

The sample size and power calculations were performed in the software EAST 6.2 and R (package "gsDesign").

3.9 SUBGROUP ANALYSES AND EFFECT OF BASELINE FACTORS

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

- Stratification factors
  - Platinum chemotherapy (cisplatin, carboplatin)
  - LDH (≤ULN, >ULN)
  - ECOG Performance Scale (0, 1)
- Age category (≤65, >65 years)
- Sex (female, male)

- Race (white, non-white)
- Smoking status (former, current)
- Brain/liver metastasis status at diagnosis (yes, no)
- Region (East Asia, non-East Asia)
- Sites of metastasis at diagnosis (<3, ≥3)
- PD-L1 expression positive (TPS<1% vs ≥1%, CPS <1 vs ≥1)

For PFS and OS, the unstratified Cox model will be used for computing the hazard ratio and its 95% CI in the subgroups. For ORR, the unstratified Miettinen and Nurminen method will be used. The consistency of the treatment effect will be assessed descriptively via summary statistics by category for the classification variables listed above. If any level of a subgroup variable has fewer than 10% of the ITT population, above analysis will not be performed for this level of the subgroup variable. If a subgroup variable has two levels and one level of the subgroup variable has fewer than 10% of the ITT population, then this subgroup will not be displayed in the forest plot. The subgroup factor platinum chemotherapy will be determined based on the platinum which was administered to a subject at the first dose. If a subject did not receive any platinum, they will be excluded from subgroup analysis. In general, a subject with a missing subgroup factor will be excluded from analysis of that subgroup.

3.10 COMPLIANCE (MEDICATION ADHERENCE)

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

3.11 EXTENT OF EXPOSURE

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

4. REFERENCES

1. Liang K, Zeger, S (2000). Longitudinal data analysis of continuous and discrete responses for pre-post designs. Sankhyā: The Indian Journal of Statistics, 62 (Series B), 134-148.
2. Maurer W, Bretz F. Multiple Testing in Group Sequential Trials using Graphical Approaches. Statistics in Biopharmaceutical Research 2013; 5(4): 311-320.
3. Miettinen O, Nurminen M. Comparative analysis of two rates. Statistics in Medicine 1985; 4:213-226.
4. Robins, J.M., Tsiatis, A.A. Correcting for non-compliance in randomized trials using rank preserving structural failure time models. Communications in Statistics-Theory and Methods, 1991; 20 (8): 2609-2631
5. Uno, H., et al. Moving Beyond the Hazard Ratio in Quantifying the Between-Group Difference in Survival Analysis. J Clin Oncol. 2014; 32 (22): 2380-2385.