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

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

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

	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																	

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).

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

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.

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.

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.

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.)	

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.

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 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			

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

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.

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

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

	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

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

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.

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

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

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

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.

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.

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.

8.6.3 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.

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