Treatment Arm	Treatment Dose and Schedule
Treatment Arm 1*	Pembrolizumab 200 mg IV Q3W Cisplatin 80 mg/m^2 IV Q3W 5-FU 800 mg/m^2/day continuous IV infusion on each of Days 1 to 5 Q3W (total of 4000 mg/m^2 per 3-week cycle) **
Treatment Arm 2*	Placebo IV Q3W Cisplatin 80 mg/m^2 IV Q3W 5-FU 800 mg/m^2/day continuous IV infusion on each of Days 1 to 5 Q3W (total of 4000 mg/m^2 per 3-week cycle) **

The body surface area in m^2 should be calculated per local guidance.

* Duration of cisplatin treatment will be capped at 6 doses; however, treatment with 5-FU may continue per local standard. 5-FU treatment is not to exceed a maximum of 35 cycles.

** Or per local standard for 5-FU administration duration as long as total dose of 4000 mg/m^2 per cycle Q3W is followed (eg, 1000 mg/m^2/day on each of Days 1 to 4). 5-FU treatment is not to exceed a maximum of 35 cycles.

Abbreviations: 5-FU=5-fluorouracil, IV=intravenous, Q3W=every 3 weeks

Study treatment in both arms will begin on Day 1 of each 3-week dosing cycle.

Beginning with screening, all imaging assessments will be submitted for central imaging vendor review and will be evaluated using Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 for determining assessment of response. On-study imaging assessments will be performed every 9 weeks (63 days ± 7 days) following the date of randomization until progression of disease is documented with radiologic imaging (computed tomography [CT] or magnetic resonance imaging [MRI]). Imaging timing should follow calendar days and should not be adjusted for delays in cycle starts.

The primary efficacy endpoints are overall survival (OS) and progression-free survival (PFS). The primary PFS analysis will be based on RECIST 1.1 by investigator assessment. RECIST 1.1 will be used by the local site for treatment decisions until verification of progressive disease (PD) by the central imaging vendor. Following verification of PD by the central imaging vendor, treatment decisions may be made by the adaptation of RECIST 1.1, as described in Section 7.1.2.5.5 – irRECIST Assessment of Disease, termed immune-related RECIST (irRECIST), to accommodate for the tumor response patterns seen with pembrolizumab treatment (eg, tumor flare). This was first described by Nishino, et al. 2013 [1], but is further modified for the programmed cell death-1 (PD-1) program. For a clinically stable subject with first radiologic evidence of PD, it is at the discretion of the site investigator to continue treating the subject with study medication until PD is confirmed at least 4 weeks from the date of the first tumor imaging suggesting PD per the site investigator. If radiologic PD is confirmed by the subsequent tumor imaging, the subject should be discontinued from treatment unless, in the opinion of the investigator, the subject is achieving a clinically meaningful benefit; an exception to continue treatment may be considered following consultation with the Sponsor.

3.1 Primary Objective(s) & Hypothesis(es)

(1) **Objective:** To compare OS between treatment arms in subjects with esophageal squamous cell carcinoma (ESCC) whose tumors are PD-L1 biomarker-positive (CPS ≥10).

Hypothesis: OS is superior with pembrolizumab plus chemotherapy compared with placebo plus chemotherapy in subjects with ESCC whose tumors are PD-L1 biomarker-positive (CPS ≥10).

(2) **Objective:** To compare OS between treatment arms in subjects with ESCC.

Hypothesis: OS is superior with pembrolizumab plus chemotherapy compared with placebo plus chemotherapy in subjects with ESCC.

(3) **Objective:** To compare OS between treatment arms in subjects whose tumors are PD-L1 biomarker-positive (CPS ≥10).

Hypothesis: OS is superior with pembrolizumab plus chemotherapy compared with placebo plus chemotherapy in subjects whose tumors are PD-L1 biomarker-positive (CPS ≥10).

(4) **Objective:** To compare OS between treatment arms in all subjects.

Hypothesis: OS is superior with pembrolizumab plus chemotherapy compared with placebo plus chemotherapy in all subjects.

(5) **Objective:** To compare PFS per RECIST 1.1, as determined by investigator, in subjects with ESCC.

Hypothesis: PFS per RECIST 1.1, as determined by investigator, is superior with pembrolizumab plus chemotherapy compared with placebo plus chemotherapy in subjects with ESCC.

(6) **Objective:** To compare PFS per RECIST 1.1, as determined by investigator, between treatment arms in subjects whose tumors are PD-L1 biomarker-positive (CPS ≥10).

Hypothesis: PFS per RECIST 1.1, as determined by investigator, is superior with pembrolizumab plus chemotherapy compared with placebo plus chemotherapy in subjects whose tumors are PD-L1 biomarker-positive (CPS ≥10).

(7) **Objective:** To compare PFS per RECIST 1.1, as determined by investigator, between treatment arms in all subjects.

Hypothesis: PFS per RECIST 1.1, as determined by investigator, is superior with pembrolizumab plus chemotherapy compared with placebo plus chemotherapy in all subjects.

The study is considered to have met its primary objective if at least one of the above hypothesis is significant as defined in Section 8.8 – Multiplicity.

3.2 Secondary Objective(s) & Hypothesis(es)

Key Secondary Objective & Hypothesis:

(1) **Objective**: Evaluate ORR per RECIST 1.1, as determined by investigator, between treatment arms in all subjects.

Hypothesis: ORR per RECIST 1.1, as determined by investigator, is superior with pembrolizumab plus chemotherapy compared with placebo plus chemotherapy in all subjects.

Other Secondary Objectives:

(2) **Objective**: Evaluate ORR per RECIST 1.1, as determined by investigator, between treatment arms in subjects with ESCC whose tumors are PD-L1 biomarker-positive (CPS ≥10), in subjects with ESCC, and in subjects whose tumors are PD-L1 biomarker-positive (CPS ≥10).

(3) **Objective**: Evaluate DOR per RECIST 1.1, as determined by investigator, between treatment arms in all subjects, in subjects with ESCC whose tumors are PD-L1 biomarker-positive (CPS ≥10), in subjects with ESCC, and in subjects whose tumors are PD-L1 biomarker-positive (CPS ≥10).

(4) **Objective**: Evaluate the safety and tolerability profile.

(5) **Objective:** To evaluate changes from baseline in health-related quality of life using the European Organization for the Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire C30 (QLQ-C30) and the EORTC Quality Of Life Questionnaire Oesophageal Module (QLQ-OES18) in all subjects, in subjects with ESCC whose tumors are PD-L1 biomarker-positive (CPS ≥10), in subjects with ESCC, and in subjects whose tumors are PD-L1 biomarker-positive (CPS ≥10), treated with pembrolizumab plus chemotherapy compared with placebo plus chemotherapy.

Exploratory Objectives:

(1) **Objective**: To characterize PRO utilities using EuroQoL 5-dimension 5-level (EQ-5D-5L) questionnaire in all subjects, in subjects with ESCC whose tumors are PD-L1 biomarker-positive (CPS ≥10), in ESCC subjects, and in subjects whose tumors are PD-L1 biomarker-positive (CPS ≥10) treated with pembrolizumab plus chemotherapy compared with placebo plus chemotherapy.

(2) **Objective**: Evaluate PFS per irRECIST as determined by investigator between treatment arms in subjects with ESCC whose tumors are PD-L1 biomarker-positive (CPS ≥10), in ESCC subjects, in subjects whose tumors are PD-L1 biomarker-positive (CPS ≥10), and in all subjects.

(3) **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 and other treatments. This could include the evaluation of microsatellite instability (MSI), whole exome sequencing (WES), and/or gene expression profiling (GEP) in available tumor tissue. Note: this is not applicable to China.

4.0 BACKGROUND & RATIONALE

4.1 Background

Pembrolizumab is a potent humanized immunoglobulin G4 monoclonal antibody with high specificity of binding to the PD-1 receptor, thus inhibiting its interaction with PD-L1 and programmed cell death-ligand 2 (PD-L2). Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an intravenous (IV) immunotherapy for advanced malignancies. Keytruda™ (pembrolizumab) is indicated for the treatment of patients across a number of indications. For more details on specific indications refer to the Investigator's Brochure (IB).

4.1.1 Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance function in controlling outgrowth of neoplastic transformations has been known for decades [2]. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells/FoxP3+ regulatory T-cells correlates 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 reinfused, inducing durable objective tumor responses in cancers such as melanoma [3] [4].

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene PDCD1) is an immunoglobulin superfamily member related to cluster of differentiation 28 and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) that has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) [5] [6].

The structure of murine PD-1 has been resolved [7]. PD-1 and its family members are type 1 transmembrane glycoproteins containing an Ig variable–type domain responsible for ligand binding and a cytoplasmic tail responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif, and an immunoreceptor tyrosine-based switch motif. Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases, SHP-1 and SHP-2, to the immunoreceptor tyrosine-based switch motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3 zeta, protein kinase C-theta, and zeta-chain-associated protein kinase, which are involved in the CD3 T-cell signaling cascade [8] [9] [10] [6]. The mechanism by which PD-1 down-modulates T-cell responses is similar to, but distinct from, that of CTLA-4, because both molecules regulate an overlapping set of signaling proteins [11] [12]. As a consequence, the PD-1/PD-L1 pathway is an attractive target for therapeutic intervention in advanced/metastatic esophageal cancer.

this trial will use a dual endpoint of OS and PFS. Progression-free survival is an acceptable measure of clinical benefit for a late stage trial that demonstrates superiority of a new antineoplastic therapy, especially if the magnitude of the effect is large and the therapy has an acceptable risk/benefit profile.

The use of a central imaging vendor and RECIST 1.1 to assess PFS is typically considered acceptable by regulatory authorities. Images will be read by a central imaging vendor blinded to treatment assignment to minimize bias in the response assessments. In addition, the final determination of radiologic progression will be based on the central assessment of progression, rather than a local site investigator/radiology assessment. Real-time determination of radiologic progression as determined by central review will be communicated to the site. Standard RECIST 1.1 will be used by the local site for treatment decisions until the occurrence of PD that is verified by the central imaging vendor.

Following verification of PD by the central imaging vendor, treatment decision may be made by the adaptation of RECIST 1.1, as outlined in Section 7.1.2.5.5 – irRECIST Assessment of Disease and termed irRECIST. Immunotherapeutic agents such as pembrolizumab may produce antitumor effects by potentiating endogenous cancer-specific immune responses, which may be functionally anergic. Recruitment of immune cells to tumor sites may result in a transient increase in the size of existing tumor lesions or the appearance of new lesions. Standard RECIST may not accurately capture the response to immunotherapeutic agents such as pembrolizumab. When feasible, subjects should not be discontinued until progression is confirmed by subsequent tumor imaging as assessed by the investigator. This allowance to continue treatment despite initial radiologic progression takes into account the observation that some subjects can have a transient tumor flare in the first few months after the start of immunotherapy but with subsequent disease response.

Change in primary endpoint of PFS from BICR to investigator-assessed

Based on recent medical monitoring review, there was greater than anticipated discordance rate (~27%) between blinded independent central review (BICR)-assessed PD and investigator-assessed PD. This has led to a higher than expected censoring of PFS events; in many of these instances, investigators decided to initiate next line of treatment without PD confirmation by BICR. The investigator assessment is based on patient's overall status including signs of clinical progression factored into their assessment of radiographic PD while BICR assessment of PD is solely based on radiographic progression. Sponsor, investigators and central readers are blinded to study treatment. Thus, the protocol is amended for the PFS endpoint to be changed from BICR-assessment to investigator-assessment.

4.2.3.1.2 Secondary Efficacy Endpoints

Objective response rate based on RECIST 1.1 and assessed by investigator, as well as DOR based on RECIST 1.1 assessed by investigator, are commonly accepted endpoints by both regulatory authorities and the oncology community.

4.2.3.1.2.1 Immune-related RECIST

RECIST 1.1 will be adapted to account for the unique tumor response characteristics seen following the treatment of pembrolizumab. Immunotherapeutic agents such as pembrolizumab may produce antitumor effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents, and subjects may manifest a clinical response after an initial increase in tumor burden or even the appearance of new lesions. Standard RECIST 1.1 may, therefore, not provide an accurate response assessment of immunotherapeutic agents such as pembrolizumab.

Based on an analysis of subjects with melanoma enrolled in KN001, 7% of evaluable subjects experienced delayed or early tumor pseudo-progression. Of note, subjects who had PD by RECIST 1.1, but not by irRECIST, had longer OS than subjects with PD by both criteria. Additionally, the data suggest that RECIST 1.1 may underestimate the benefit of pembrolizumab in approximately 15% of subjects. These findings support the need to apply a modification to RECIST 1.1 that takes into account the unique patterns of atypical response in immunotherapy and enables treatment beyond initial radiographic progression.

The irRECIST assessment is based on RECIST 1.1 and is adapted to account for the unique tumor response seen with immunotherapeutics as described by Nishino et al. [1]. The assessment of unidimensional target lesions and response categories per irRECIST are identical to RECIST 1.1. However, the Sponsor has implemented an adaptation related to new lesions, non-target lesions, and tumor burden assessment in order to confirm radiographic progression. irRECIST will be used by local site investigators to assess tumor response and progression and to make treatment decisions, as well as to be used by the central imaging vendor in support of the PFS endpoint.

For further information on irRECIST, see Section 7.1.2.5.5– irRECIST Assessment of Disease.

4.2.3.2 Rationale for Patient-reported Outcomes

Symptomatic improvement is considered a clinical benefit and accepted by health authorities as additional evidence on the risk-benefit profile of any new treatment. As part of the analyses for this trial, subjects will provide information regarding their health-related quality of life via the following assessment tools: EORTC QLQ-C30, EORTC QLQ-OES18, and EuroQol EQ-5D-5L. These measures are not pure efficacy or safety endpoints because they are affected by both disease progression and treatment tolerability. Details on these instruments are provided in Section 7.1.2.6.2 – Electronic Patient-reported Outcomes.

4.2.3.3 Rationale for Safety Endpoints

Safety parameters commonly used for evaluating investigational systemic anticancer treatments are included as safety endpoints including, but not limited to, the incidence of, causality, and outcome of AEs/SAEs; and changes in vital signs and laboratory values. Adverse events will be assessed as defined by CTCAE v4.0.

4.2.3.4 Planned Biomarker Research

A PD-L1 biomarker-positive subject is defined as one whose tumor has a CPS ≥10, as defined in Section 4.2.3.4.1 – Biomarker Research for Primary Objectives.

4.2.3.4.1 Biomarker Research for Primary Objectives

PD-L1 Expression

PD-L1 protein level in tumor sections, assessed by IHC, correlates with response to pembrolizumab in patients with NSCLC, and an in vitro diagnostic device has been developed. Preliminary data indicate that this association between tumor PD-L1 expression and response to pembrolizumab may also be true in additional cancer types (eg, triple-negative breast cancer, head and neck cancer, and gastric cancer), therefore, this relationship was also evaluated in esophageal cancer. An interim database lock of a subset of KN180 subjects (N = 105) was used as training set to evaluate the utility of a PD-L1 CPS across a range of cut points in identifying subjects with esophageal cancer that respond to pembrolizumab. Combined positive score is defined as the percentage of tumor cells and mononuclear inflammatory cells within the tumor nests and the adjacent supporting stroma expressing PD-L1 at any intensity.

For those subjects that had esophageal tumor PD-L1 scores of CPS ≥10 (approximately 45% of subjects), both ORR and survival were significantly improved compared with either the all-comers population or the population with CPS <10. This cut point also maintained good sensitivity to detect responders as well as prevalence across esophageal tumors, compared with other cut points. Programmed cell death-ligand 1 CPS ≥10 will be used in KN590 as part of the primary objectives outlined in section 3.1 above.

4.2.3.4.2 Biomarker Research for Exploratory Objectives

Introduction: Cancer immunotherapies represent an important and novel class of antitumor agents. However, the mechanism of action of these exciting new therapies is not completely understood and much remains to be learned regarding how best to leverage these new drugs in treating patients. Thus, to aid future patients, it is important to investigate the determinants of response or resistance to cancer immunotherapy as well as determinants of AEs in the course of our clinical trials. These efforts will identify novel predictive/pharmacodynamic biomarkers and generate information that will better guide single-agent and combination therapy with immuno-oncology drugs. To identify novel biomarkers, biospecimens (ie, blood components, tumor material) will be collected 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, MSI may be evaluated, as this is an important biomarker for some cancers (eg, 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 (eg, mutations, methylation status, MSI). Key molecular changes of interest to immune-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. 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 (eg, colorectal cancer).

Tumor and blood RNA analyses: Both genome-wide and targeted mRNA expression profiling and sequencing in tumor tissue and in blood may be performed to define gene signatures that correlate to clinical response to treatment with pembrolizumab or other immunotherapies. Pembrolizumab induces a response in tumors that likely reflects an inflamed/immune phenotype. Specific immune-related gene sets (ie, 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 immunohistochemistry using blood or tumor: Tumor and blood samples from this study may undergo proteomic analyses. Additional tumor or blood-derived proteins may also correlate with response to pembrolizumab. Therefore, tumor tissue may be subjected to proteomic analyses using a variety of platforms that could include, but are not limited to, immunoassays and liquid chromatography/mass spectrometry. This approach could identify novel protein biomarkers that could aid in patient selection for pembrolizumab therapy.

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

Other exploratory biomarkers (eg, PD-1 expression, markers of T-cell phenotype) may also be evaluated.

Note that exploratory biomarkers are not applicable for China.

Immune-related AEs	Toxicity grade or conditions (CTCAE v4.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
AST/ALT elevation or increased bilirubin	Grade 2	Withhold	• Administer corticosteroids (initial dose of 0.5 to 1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable)
	Grade 3 or 4	Permanently discontinue	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	
T1DM or hyperglycemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold	• Initiate insulin replacement therapy for subjects with T1DM • Administer anti-hyperglycemic in subjects with hyperglycemia	• Monitor subjects for hyperglycemia or other signs and symptoms of diabetes
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hypothyroidism	Grade 2 to 4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care	• Monitor for signs and symptoms of thyroid disorders
Nephritis and renal dysfunction	Grade 2	Withhold	• Administer corticosteroids (prednisone 1 to 2 mg/kg or equivalent) followed by taper	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1 or 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		

Table 7 Dose Modification Guidelines for 5-fluorouracil Drug-Related Adverse Events

Category	Toxicity	Hold 5-FU Treatment for Grade	Timing for Restarting 5-FU Treatment	Dose for Restarting 5-FU Treatment	Discontinue 5-FU
Hematologic[c]	Neutropenia	3[a]	Neutrophil count resolves to > 1,000/mm^3	No Reduction (consider G-CSF)	Toxicity does not resolve within 4 or 5 weeks of last infusion or if > 2 dose level reductions exceeded
		4[a]	Neutrophil count resolves to > 1,000/mm^3	Reduce by 1 DL (consider G-CSF)	Toxicity does not resolve within 4 or 5 weeks of last infusion or if > 2 dose level reductions exceeded
	Febrile neutropenia	3[a]	Toxicity resolves to Grade 0 or 1	Reduce by 1 DL	Toxicity does not resolve within 4 or 5 weeks of last infusion or if > 2 dose level reductions exceeded
		4[a]	NA	Discontinue	Permanently discontinue
	Thrombo-cytopenia	3 or 4[a]	Platelet count resolves to > 75,000/mm^3	Reduce by 1 DL	Toxicity does not resolve within 4 or 5 weeks of last infusion or if > 2 dose level reductions exceeded
Non-hematologic	Diarrhea, mucositis, or hand-foot syndrome	2 or 3	Toxicity resolves to Grade 0 or 1	Reduce by 1 DL	Toxicity does not resolve within 4 or 5 weeks of last infusion or if > 2 dose level reductions exceeded
		4	NA	Discontinue	Permanently discontinue
	All other non-hematologic toxicities[b]	3 or 4[a]	Toxicity resolves to Grade 0 or 1	Reduce by 1 DL	Toxicity does not resolve within 4 or 5 weeks of last infusion or if > 2 dose level reductions exceeded
	Laboratory AEs	4[a]	Toxicity resolves to Grade 0 or 1	Reduce by 1 DL	Toxicity does not resolve within 4 or 5 weeks of last infusion or if > 2 dose level reductions exceeded

[a] **Permanent discontinuation should be considered for any severe or life-threatening event. Consult Sponsor before restarting treatment after Grade 4 drug related AE.**

[b] Subjects with intolerable or persistent Grade 2 drug-related AE may hold at physician discretion. Permanently discontinue from agent for persistent Grade 2 adverse reactions for which treatment has been held, and did not recover to Grade 0 or 1 within 12 weeks of the last dose.

[c] Subjects with intolerable or persistent Grade 2 drug-related AE may hold at physician discretion.

Abbreviations: AE=adverse event, DL=dose level, G-CSF= granulocyte colony-stimulating factor, NA=not applicable.

5.2.2 Timing of Dose Administration

Study treatment in both arms will begin on Day 1 of each 3-week dosing cycle after all procedures/assessments have been completed as detailed in Section 6.0 – Trial Flow Chart. Trial treatments may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons.

All trial treatments may be administered on an outpatient basis.

Treatment will be administered in the order presented below:

- Pembrolizumab or placebo infusion is administered first, followed by the cisplatin and 5-FU infusions.

Administration of chemotherapy (ie, cisplatin and/or 5-FU) may follow 1 to 2 days after pembrolizumab/placebo (eg, Day 2 or Day 3) as needed per local standard of care.

Treatment may continue with pembrolizumab + chemotherapy or placebo + chemotherapy until documented confirmed PD, unacceptable AE(s), intercurrent illness that prevents further administration of treatment, investigator's decision to discontinue treatment, subject withdraws consent, pregnancy of the subject, noncompliance with trial treatment or procedure requirements, subject receives 35 administrations (approximately 2 years) of study medication, or administrative reasons requiring cessation of treatment.

Note: Dosing interruptions are permitted in the case of medical/surgical events or logistical reasons (i.e., elective surgery, unrelated medical events, subject vacation, and holidays) not related to study therapy. Subjects should be placed back on study therapy as soon as clinically appropriate per the investigator, and not exceeding 3 weeks from the interrupted dosing. Day 1 of subsequent cycles should be adjusted accordingly to adhere to every 3-week dosing schedule. Discuss with the Sponsor if subject cannot restart study medication within 3 weeks. The reason for interruption should be documented in the subject's study record.

5.2.2.1 Pembrolizumab

Regardless of clinical benefit, subjects may only receive 35 administrations (approximately 2 years) with pembrolizumab. Pembrolizumab 200-mg fixed dose will be administered as a 30-minute IV infusion Q3W. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is between 25 and 40 minutes). Note that infusion time may be adjusted as needed if subject has experienced an infusion reaction (see Table 5).

The Pharmacy Manual contains specific instructions for the preparation of the pembrolizumab infusion fluid and administration of infusion solution. Pembrolizumab will be prepared by unblinded qualified site personnel and administered by blinded qualified site personnel.

Trial Period	Screening Phase	Treatment Cycles								End of Treatment	Post-treatment		
Treatment Cycle/Title	**Screening (Visit 1)**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8 and Beyond**	**Discon**	**Safety Follow-up**	**Follow-Up Visits**	**Survival Follow-Up[a]**
										At time of Discon	**30 Days post Last Dose**	**Every 9 Weeks Post-discon**	**Every 12 Weeks**
Scheduling Window (Days)[b]	**-28 to -1**		**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 7**	**± 7**	**± 7**
Trial Treatment Administration													
Pembrolizumab/Placebo Administration[h,i]		X	X	X	X	X	X	X	X				
Cisplatin Administration[h,j]		X	X	X	X	X	X						
5-FU Administration[h]		X	X	X	X	X	X	X	X				
Laboratory Procedures/Assessments: Analysis Performed by LOCAL Laboratory													
Pregnancy Test[k]	X												
PT/INR and aPTT	X[f]												
CBC with Differential[l]	X[f]		X	X	X	X	X	X	X	X	X		
Chemistry Panel[l]	X[f]		X	X	X	X	X	X	X	X	X		
Urinalysis[l]	X[f]		X		X		X		X	X			
T3, FT4, and TSH[l]	X		X		X		X		X	X	X		
Laboratory Procedures/Assessments: Analysis Performed by CENTRAL Laboratory (not applicable for China)													
Pembrolizumab Pharmacokinetics[m]		X	X		X								
Pembrolizumab Anti-Drug Antibodies[m]		X	X		X								
Blood for Genetic Analysis[n]		X											
Blood for RNA Analyses[o]		X	X			X				X			

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 in the medical history. Additional time points may be performed as clinically necessary.

7.1.2.5 Tumor Imaging and Assessment of Disease

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

Subject eligibility will be determined using local assessment (investigator assessment) based on RECIST 1.1. Although RECIST 1.1 references a maximum of 5 target lesions in total and 2 per organ, the Sponsor allows a maximum of 10 target lesions in total and 5 per organ. All scheduled images for all trial subjects from the sites will be submitted to the central imaging vendor. In addition, images (including via other modalities) that are obtained at an unscheduled time point to determine PD, as well as imaging obtained for other reasons, but captures radiologic progression, should also be submitted to the central imaging vendor.

The central imaging vendor will verify PD following the first radiologic evidence of PD (based on local investigator assessment). Expedited verification of radiologic PD by the central imaging vendor will be communicated to the trial site and Sponsor (see Section 7.1.2.5.2 – Tumor Imaging During the Trial).

7.1.2.5.1 Initial Tumor Imaging

Initial tumor imaging at Screening must be performed within 21 days prior to the date of randomization. The site trial team must review screening images to confirm the subject has measurable disease per RECIST 1.1.

The screening images must be submitted to the central imaging vendor for retrospective review.

Scans performed as part of routine clinical management are acceptable for use as screening tumor imaging if they are of diagnostic quality and performed within 21 days prior to the date of randomization and can be assessed by the central imaging vendor. At sites where the local regulatory body and/or IRB/ERC will not permit a second tumor imaging within a 21-day period, an already available imaging scan obtained within 28 days prior to first dose may be used with the approval of the Sponsor Clinical Director.

Subjects with previously treated brain metastases may participate provided they have stable brain metastases (ie, without evidence of progression by imaging as confirmed by MRI if MRI was used at prior imaging or confirmed by CT imaging if CT was used at prior imaging for at least 4 weeks prior to the first dose of trial treatment). Any neurologic symptoms must have returned to baseline and subjects must have no evidence of new or enlarging brain metastases and have not used steroids for brain metastases for at least 14 days prior to trial

7.1.2.6.2.2 EORTC QLQ-C30

The EORTC QLQ-C30 was developed to assess the quality of life of patients with cancer. It has been translated and validated into 81 languages and used in more than 3000 studies worldwide. It consists of 5 functioning scales (physical, role, cognitive, emotional, and social), 3 symptom scales (fatigue, nausea, pain), and additional single-symptom items [32]. 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 a 7-point scale scoring with anchors (the scores range from 1=very poor to 7=excellent).

7.1.2.6.2.3 EORTC QLQ-OES18

The EORTC QLQ-OES18 is a disease-specific questionnaire developed and validated to address measurements specific to esophageal cancer [33]. It is one of multiple disease-specific modules developed by the EORTC Quality of Life Group designed for use in clinical trials, to be administered in addition to the QLQ-C30 to assess disease-specific treatment measurements. It contains 18 items with symptoms of dysphagia, pain, reflux, eating, difficulty with swallowing saliva, choking, dry mouth, taste, cough, and speech.

7.1.3 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below. The total amount of blood/tissue to be drawn/collected over the course of the trial (from pre-trial to post-trial visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per subject can be found in the Trial Procedures Manual. Refer to Section 6 – Trial Flow Chart for the timing of laboratory assessments.

7.1.3.1 Laboratory Safety Evaluations (Hematology, Chemistry, and Urinalysis)

Laboratory tests for hematology, chemistry, and urinalysis are specified in Table 9.

Table 9 Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Blood	Pregnancy test (serum or urine)[a]
Hemoglobin	Alkaline phosphatase	Glucose	Prothrombin Time (PT) or International Normalized Ratio (INR)
Platelet count	ALT (SGPT)	Protein	Activated Partial Thromboplastin Time (aPTT)
White blood cell (WBC) (total and differential)[b]	AST (SGOT)	Specific gravity	Total triiodothyronine (T3) or Free T3[c,d]
Red blood cell (RBC) count	Bicarbonate (or carbon dioxide [CO_2])[e]	Microscopic exam, if abnormal results are noted	Free thyroxine (FT4)[d]
Absolute lymphocyte count	Calcium		Thyroid-stimulating hormone (TSH)[d]
Absolute neutrophil count (ANC)	Chloride		
	Creatinine or creatinine clearance[f]		
	Glucose		
	Phosphorus		
	Potassium		
	Sodium		
	Total bilirubin		
	Direct bilirubin, if total bilirubin is elevated above the upper limit of normal		
	Total protein		
	Blood urea nitrogen (BUN)/urea[g]		

a. For women of reproductive potential, a urine or serum pregnancy test must be performed within 72 hours prior to randomization. If first dose of study treatment occurs > 72 hours after randomization, pregnancy test must be repeated to be within 72 hours of first dose of study treatment. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required. Monthly pregnancy testing should be conducted as per local regulations where applicable.
b. Report % or absolute results for differential per standard of practice. Report the results in the same manner throughout the trial.
c. Total T3 is preferred; if not available, free T3 may be tested.
d. 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 Procedures Manual. Note, there may be instances when sites are unable to obtain the thyroid function testing results prior to scheduled dosing. After Cycle 1, review of thyroid function tests (FT3, FT4 and TSH) results after dosing is acceptable.
e. If these tests are not done as part of standard of care in your region, then these tests do not need to be performed.
f. Glomerular filtration rate can also be used in place of creatinine or creatinine clearance
g. BUN is preferred; if not available, urea may be tested.

Abbreviations: ALT (SGPT)=alanine aminotransferase (serum glutamic pyruvic transaminase); AST (SGOT)=aspartate aminotransferase (serum glutamic oxaloacetic transaminase)

Laboratory tests for screening should be performed within 14 days prior to the first dose of trial treatment. An exception is hepatitis (if required per local regulations) and thyroid

7.1.3.4.2 Blood Collection for Anti-pembrolizumab Antibodies

Pre-dose anti-pembrolizumab antibodies samples will be collected at Cycles 1, 2 and 4 for the first approximately 100 randomized subjects. All pre-dose trough samples should be drawn within 24 hours before infusion of pembrolizumab/placebo. Sample collection, storage, and shipment instructions for serum samples will be provided in the Procedures Manual.

Note that no samples should be collected from subjects randomized after 31-Jan-2018, including all subjects from China.

7.1.3.4.3 Blood Collection for RNA Analysis and Plasma and Serum Biomarker Analyses

Blood should be collected pre-dose for Cycles 1, 2, 5 and at the time of discontinuation. Leftover RNA, plasma, and serum will be stored at the end of the trial for Future Biomedical Research (FBR) if the subject has consented (see Section 4.2.3.5 – Future Biomedical Research).

Further details are provided in the Procedures Manual.

Note that these samples are not applicable to China.

7.1.3.5 Planned Genetic Analysis Sample Collection

Sample collection, storage and shipment instructions for Planned Genetic Analysis samples will be provided in the Procedures Manual. Samples should be collected for planned analysis of associations between genetic variants in germline/tumor DNA and drug response. If a documented law or regulation prohibits (or local IRB/ERC does not approve) sample collection for these purposes, then such samples should not be collected at the corresponding sites. Leftover DNA extracted from planned genetic analysis samples will be stored for future biomedical research only if subject signs the FBR consent. Note that this is not applicable to China.

7.1.3.6 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 main study tumor tissue

7.1.3.7 Tumor Tissue

Eligibility for this study is dependent upon supplying tumor tissue for biomarker analysis as described under eligibility criteria. Repeat samples may be required if adequate tissue is not provided. If the subject signs the FBR consent, any leftover tissue that would ordinarily be discarded at the end of the main study will be retained for FBR.

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

7.2 Assessing and Recording Adverse Events

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

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

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

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

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

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

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

Adverse events will not be collected for subjects during the pre-screening period (for determination of archival tissue status) as long as that subject has not undergone any protocol-specified procedure or intervention. If the subject requires a blood draw, fresh

tumor biopsy etc., the subject is first required to provide consent to the main study and AEs will be captured according to guidelines for standard AE reporting.

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

For purposes of this trial, an overdose will be defined as any dose exceeding the prescribed dose for cisplatin or 5-FU by ≥ 20% and as ≥ 1000 mg (5 times the dose) of pembrolizumab in a 3-week period. No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, study treatment should be discontinued and the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

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

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

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

7.2.2 Reporting of Pregnancy and Lactation to the Sponsor

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

Pregnancies and lactations that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure. Pregnancies and lactations that occur from the time of treatment allocation/randomization through 120 days following cessation of Sponsor's product, or 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.

period specified in the paragraph above, or at any time outside of the time period specified in the previous paragraph also must be reported immediately to the Sponsor.

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

7.2.3.2 Events of Clinical Interest

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

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

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

Events of clinical interest for this trial include:

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

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

7.2.3.3 Protocol-Specific Exceptions to Serious Adverse Event Reporting

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

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

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

7.2.4 Evaluating Adverse Events

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

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

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

discontinuation of the study, this EOC may be unblinded to results at the treatment level in order to act on these recommendations. If the EOC is unblinded to the results, they may consult with Sponsor Senior Management to determine if further actions need to be taken. Additional Sponsor personnel may be unblinded to the treatment level results of the main PFS analyses, if required, in order to act on the recommendations of the DMC or facilitate regulatory filing after the first PFS analysis. The extent to which individuals are unblinded with respect to the results of the IA will be documented by the unblinded statistician

8.0 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, changes made to primary and/or key secondary hypotheses, or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with ICH Guideline 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. There will be a separate PK analysis plan as well as biomarker analysis plan. Post hoc exploratory analyses will be clearly identified in the CSR. The PRO analysis plan will be included in the sSAP.

8.1 Statistical Analysis Plan Summary

Key elements of the statistical analysis plan that are summarized below are applicable to the Global Study population (all enrolled subjects N=749). The comprehensive plan is provided in Section 8.2 – Responsibility for Analyses/In-house Blinding through Section 8.12 – Extent of Exposure. Additional details for the statistical analysis of the China Cohort (N=106) are described in the supplemental SAP.

Study Design Overview	A Randomized, Double-Blind, Placebo-Controlled Phase III Clinical Trial of Pembrolizumab (MK-3475) in Combination with Cisplatin and 5-Fluorouracil versus Placebo in Combination with Cisplatin and 5-Fluorouracil as First-Line Treatment in Subjects with Advanced/Metastatic Esophageal Carcinoma (KEYNOTE-590)
Treatment Assignment	Subjects will be randomized in a 1:1 ratio to receive pembrolizumab with 5-fluorouracil (5-FU) and cisplatin combination therapy or placebo with 5-FU and cisplatin. Stratification factors are in Section 5.4 – Stratification.
Analysis Populations	Global Study Population N=749 Efficacy: Intention to Treat Safety: All Subjects as Treated
Primary Endpoints/Hypotheses	1. OS in subjects with ESCC whose tumors are PD-L1 biomarker-positive (CPS ≥10). 2. OS in subjects with ESCC. 3. OS in subjects whose tumors are PD-L1 biomarker-positive (CPS ≥10). 4. OS in all subjects. 5. PFS based on RECIST 1.1 as assessed by investigator in subjects with ESCC. 6. PFS based on RECIST 1.1 as assessed by investigator in subjects whose tumors are PD-L1 biomarker-positive (CPS ≥10). 7. PFS based on RECIST 1.1 as assessed by investigator in all subjects.

Overall Survival

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

8.4.1.2 Secondary Efficacy Endpoints

Objective Response Rate – RECIST 1.1 by investigator assessment

Objective response rate is defined as the proportion of the subjects in the analysis population who have a CR or PR.

Duration of Response – RECIST 1.1 by investigator assessment

For subjects who demonstrate CR or PR, DOR is defined as the time from first documented evidence of CR or PR until disease progression per RECIST 1.1 based on assessments by investigator or death due to any cause, whichever occurs first. See Section 8.6.1.4 – Duration of Response for the definition of censoring.

8.4.2 Safety Endpoints

Safety measurements are described in Section 7 – Trial Procedures.

8.4.3 Patient-reported Outcome Endpoints

Assessment of PRO will be based on the EORTC QLQ-C30 and 3 pre-specified disease-related symptom scores (dysphagia, reflux, and pain) from the EORTC QLQ-OES18.

Time to deterioration (10 points worse than baseline) and rate of improvement (10 points better than baseline) in EORTC QLQ-C30 global health status, and the 3 pre-specified disease-related symptom scores from the EORTC QLQ-OES18 will be analyzed.

8.5 Analysis Populations

8.5.1 Efficacy Analysis Populations

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

The ITT population for the primary analyses is the Global Study population (N=749) which includes all subjects randomized in the Global Study. Details on the approach to handling missing data are provided in Section 8.6 – Statistical Methods.

8.5.2 Safety Analysis Populations

The All Subjects as Treated (ASaT) population will be used for the analysis of safety data in this study. The ASaT population consists of all randomized subjects who received at least

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

At least 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.

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

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.

Note that a sensitivity analysis for efficacy endpoints described in Sections 8.6.1.1 through 8.6.1.4 below will also be conducted for the Global Cohort (N=711).

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

8.6.1.1 Progression-free Survival

The non-parametric Kaplan-Meier method will be used to estimate the PFS rate over time in each treatment group. The hypotheses of treatment difference in PFS will be tested by the stratified log-rank test. A stratified Cox proportional hazard model with Efron's method of tie handling will be used to estimate the magnitude of the treatment difference (ie, hazard ratio [HR]) between the treatment arms. The HR and its 95% confidence interval (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 – Stratification) 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 PD will be approximated by the date of the first assessment at which PD is objectively documented

Table 12 Censoring Rules for Duration of Response

Situation	Date of Progression or Censoring	Outcome
No progression nor death, no new anticancer therapy initiated	Last adequate disease assessment	Censor (Non-event)
No progression nor death, new anticancer therapy initiated	Last adequate disease assessment before new anticancer therapy initiated	Censor (Non-event)
≥ 2 consecutive missed disease assessments at any time prior to progression or death	Last adequate disease assessment prior to ≥ 2 missed adequate disease assessments	Censor (Non-event)
Death or progression after ≤ 1 missed disease assessment	PD or death	End of response (Event)
A missed disease assessment includes any assessment that is not obtained or is considered inadequate for evaluation of response. Subjects are considered to have an ongoing response if censored, alive, have not progressed, have not started a new anticancer therapy, have not had ≥ 2 consecutive missed disease assessments, and have not been determined to be lost to follow-up. Abbreviations: PD=progressive disease		

The primary approach for DOR will be based on RECIST 1.1 by investigator assessment. A sensitivity analysis using RECIST 1.1 by BICR will also be conducted.

Table 13 summarizes the primary analysis approach for primary and key secondary efficacy endpoints. Sensitivity analysis methods are described above for each endpoint.

The strategy to address multiplicity issues with regard to multiple efficacy endpoints, multiple populations, and the IA is described in Section 8.7 – Interim Analyses and in Section 8.8 – Multiplicity.

Tier 2 parameters will be assessed via point estimates with 95% CIs provided for differences in the proportion of participants with events using the Miettinen and Nurminen method, an unconditional, asymptotic method [39].

Membership in Tier 2 requires that at least 5% of participants 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 5% of participants was chosen for Tier 2 events because the population enrolled in this study is in critical condition and usually experiences various AEs of similar types regardless of treatment; events reported less frequently than 5% of participants would obscure the assessment of the overall safety profile and add little to the interpretation of potentially meaningful treatment differences. In addition, Grade 3 to 5 AEs (≥5% of participants in 1 of the treatment groups) and SAEs (≥2% of participants in 1 of the treatment groups) will be considered Tier 2 endpoints. 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 as a formal method for assessing the statistical significance of the between-group differences.

Safety endpoints that are not Tier 1 or 2 events are considered Tier 3 events. The broad AE categories consisting of the proportion of participants with any AE, a drug related AE, a serious AE, an AE which is both drug-related and serious, a Grade 3-5 AE, a drug-related Grade 3-5 AE, and discontinuation due to an AE will be considered Tier 3 endpoints. Only point estimates by treatment group are provided for Tier 3 safety parameters.

Table 14 Analysis Strategy for Safety Parameters

Safety Tier	Safety Endpoint	p-Value	95% CI for Treatment Comparison	Descriptive Statistics
Tier 2	Grade 3-5 AE (incidence ≥5% of participants in one of the treatment groups)		X	X
	Serious AE (incidence ≥2% of participants in one of the treatment groups)		X	X
	AEs (incidence ≥5% of participants in one of the treatment groups)		X	X
Tier 3	Any AE			X
	Any Grade 3-5 AE			X
	Any Serious AE			X
	Any Drug-Related AE			X
	Any Serious and Drug-Related AE			X
	Any Grade 3-5 and Drug-Related AE			X
	Discontinuation due to AE			X
	Death			X
	Specific AEs, SOCs (incidence ≥0% of participants in 1 of the treatment groups)			X
	Change from Baseline Results (lab toxicity shift, vital signs)			X
Abbreviations: AE = adverse event; CI = confidence interval; SOC = system organ class.				

assessment typically associated with a planned efficacy IA, because these analyses are not to declare a positive efficacy finding based on these results.

8.9 Sample Size and Power Calculations

The sample size and power calculations for PFS and OS assume the following:

- PFS follows an exponential distribution with a median of 6 months for the control group.
- OS follows an exponential distribution with a median of 12 months for the control group.
- Enrollment period of 22 months
- An annual dropout rate of 5% for both PFS and OS

The sample size and power calculations were performed using R ("gsDesign" package).

Note, at the time of this amendment, the study enrollment has been completed. The study has enrolled 749 subjects in a 1:1 ratio into the pembrolizumab + chemotherapy and the placebo + chemotherapy arms. PFS and OS are primary endpoints for the study, with ORR as the key secondary endpoint. It is expected that the prevalence of ESCC with PD-L1 CPS ≥10 is 38%, PD-L1 CPS ≥10 is 51% (all subjects), and ESCC is 73%.

For the PFS endpoint, based on a target number of 460 investigator-assessed events in ESCC at IA (final for PFS), the study has approximately 82.8% power to detect an HR of 0.7 at an overall α level of 0.002 (1-sided).

In the scenario that the PFS hypothesis is rejected in ESCC, the PFS test has 62.2% power to detect an HR of 0.7 at an α level of 0.002 in subjects with PD-L1 CPS ≥10. In the scenario that both of PFS hypotheses in ESCC and in PD-L1 CPS ≥10 are rejected, the PFS test has 76.8% power to detect an HR of 0.75 at an α level of 0.002 in all subjects. In the scenario that the PFS null hypotheses in all populations and all OS null hypotheses are rejected, the PFS test has 95.1% power to detect an HR of 0.75 at an α level of 0.025 in all subjects.

For the OS endpoint, based on a target number of 233 events and 1 interim analysis at approximately 86% of the target number of events, the study has approximately 84.5% power at FA to detect an HR of 0.65 at an overall α level of 0.012 (1-sided) in ESCC subjects with PD-L1 CPS ≥10; and based on a target number of 455 events, the study has approximately 88.3% power at FA to detect an HR of 0.72 at an overall α level of 0.011 (1-sided) in ESCC subjects.

Abbreviation/Term	Definition
EQ-5D-5L	EuroQol 5-dimension 5-level questionnaire
ERC	Ethics Review Committee
ESCC	esophageal squamous cell carcinoma
ESMO	European Society for Medical Oncology
EU	European Union
FBR	Future Biomedical Research
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FSH	follicle-stimulating hormone
FT4	free thyroxine
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
GEP	gene expression profile
GI	gastrointestinal
HEENT	head, eyes, ears, nose, and throat
HER-2/neu	human epidermal growth factor receptor-2
HGRAC	Human Genetics Resources Administration of China
HIV	human immunodeficiency virus
HR	hazard ratio
HRQoL	health-related quality of life
IA	interim analysis
IA	interim analysis
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IHC	immunohistochemistry
irAE	immune-related adverse event
INR	international normalized ratio
IRB	Institutional Review Board
irRECIST	immune-related Response Evaluation Criteria in Solid Tumors
ITT	intent-to-treat
IV	intravenous
IVRS	interactive voice response system
IWRS	integrated web response system

Treatment will continue until confirmed PD, unacceptable adverse events (AEs), intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw the subject, subject withdraws consent, pregnancy of the subject, noncompliance with trial treatment or procedure requirements, completion of 35 administrations (approximately 2 years) of treatment with study medication or achievement of a complete response (CR), or administrative reasons.

AEs will be monitored throughout the trial and graded in severity according to the guidelines outlined in the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 (v4.0). At the end of treatment, each subject will be followed for a minimum of 30 days for AE monitoring. Serious adverse events (SAEs) occurring within 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, will be collected, whichever is earlier. Subjects who discontinue treatment for reasons other than PD will have post-treatment follow-up for disease status until PD, initiating a non-study cancer treatment, withdrawing consent, or becoming lost to follow-up. All subjects will be followed by telephone contact for OS until death, withdrawal of consent, or the end of the trial, whichever comes first.

This study will be conducted in conformance with Good Clinical Practice (GCP).

This trial will use a group sequential design based on pre-specified criteria, using an independent, external Data Monitoring Committee (DMC) to monitor safety and efficacy. There will be one efficacy interim analysis (IA) for OS which will also be the final analysis (FA) for PFS and periodic safety monitoring. The efficacy IA is event-driven. If all OS and PFS hypotheses are rejected, objective response rate (ORR) will also be tested. Results of the efficacy IA will be reviewed by the DMC. More details are in Section 8.7 – Interim Analyses.

No crossover from placebo arm to pembrolizumab arm will be allowed.

The China Cohort

Approximately 106 eligible subjects from China will be enrolled in the China Cohort. This will include subjects enrolled in China during the Global enrollment period as well as the China Extension Study enrollment period. After the enrollment of the Global Cohort is closed, subjects from China will continue to be enrolled in the China Extension study until a total of 106 subjects from China are enrolled. The China Extension study will be identical to the Global Cohort with respect to key study characteristics (eg, inclusion and exclusion criteria, study endpoints, primary and secondary objectives, study procedures). The Global Cohort and China Extension study will be merged for the primary analyses, and henceforth will be referred to as the Global Study population. Further details of the analyses in this Cohort are provided in the supplemental SAP.

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

2.2 Trial Diagram

The trial design is depicted in Figure 1.

4.1.2 Pre-clinical and Clinical Trials

Therapeutic studies in mouse models have shown that administration of antibodies blocking PD-1/PD-L1 interaction enhances infiltration of tumor-specific CD8+ T-cells and leads ultimately to tumor rejection, either as a monotherapy or in combination with other treatment modalities. Anti-mouse PD-1 or anti-mouse PD-L1 antibodies have demonstrated antitumor responses as a monotherapy in models of squamous cell carcinoma, pancreatic carcinoma, melanoma, and colorectal carcinoma. Blockade of the PD-1 pathway effectively promoted CD8+ T-cell infiltration into the tumor and the presence of interferon gamma, granzyme B, and perforin, indicating that the mechanism of action involved local infiltration and activation of effector T-cell function in vivo [13] [3] [4] [14] [6] [5]. Experiments have confirmed the in vivo efficacy of PD-1 blockade as a monotherapy as well as in combination with chemotherapy in syngeneic mouse tumor models (see the IB for further details).

Clinical trials have demonstrated efficacy in subjects with advanced melanoma, non-small cell lung cancer (NSCLC), head and neck cancer, bladder cancer, Hodgkin's lymphoma, triple-negative breast cancer, and gastric adenocarcinoma.

4.1.3 Ongoing Clinical Trials

Ongoing clinical trials of pembrolizumab are being conducted in advanced melanoma, NSCLC, and a number of other advanced solid tumor indications and hematologic malignancies. For details on all ongoing pembrolizumab studies, refer to the IB.

4.1.3.1 Ongoing Clinical Trials in Esophageal Cancer

Two trials are currently ongoing with pembrolizumab in esophageal cancer. KEYNOTE (KN) 180 is a Phase II study of pembrolizumab monotherapy in third-line previously treated subjects with advanced/metastatic adenocarcinoma or squamous cell carcinoma of the esophagus or advanced/metastatic Siewert type 1 adenocarcinoma of the EGJ. This open-label trial completed enrollment 21-Mar-2017 with 121 subjects allocated to treatment. The second study, KN181, is a Phase III, randomized, open-label study of single-agent pembrolizumab versus physicians' choice of single-agent docetaxel, paclitaxel, or irinotecan in subjects with advanced/metastatic adenocarcinoma and squamous cell carcinoma of the esophagus or advanced/metastatic Siewert type 1 adenocarcinoma of the EGJ that have progressed after first-line standard therapy. As of 16-Jun-2017, KN181 has completed enrollment of 629 subjects in the global cohort out of a total of approximately 600 planned.

4.1.4 Information on Other Trial-related Therapy

Cisplatin is a platinum-based chemotherapy that acts by interfering with DNA replication, and 5-FU is a fluoropyrimidine that interferes with DNA synthesis to inhibit tumor growth. Cisplatin and 5-FU are currently recommended by guidelines for first-line treatment of subjects with advanced/metastatic esophageal cancer. Refer to the respective product labels and Section 4.2.2.1 – Justification for Treatment Regimen for further information.

4.2.3.5 Future Biomedical Research

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

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

Note: Future Biomedical Research is not applicable for China.

4.3 Benefit/Risk

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

Beneficial effects of pembrolizumab have been seen in several trials to date. Publications of a significantly positive benefit/risk ratio have been reported for melanoma both in a single-arm study encompassing nearly 1000 patients (KN001), which led to United States FDA approval in September 2014, and in a randomized comparison to chemotherapy (KN002 – detailed in the IB). Data from KN028, a Phase 1b study in subjects with esophageal cancer, also support a positive benefit/risk ratio (see Section 4.2.1 – Rationale for the Trial and Selected Subject Population).

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

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

Male and female subjects with locally advanced unresectable or metastatic adenocarcinoma or squamous cell carcinoma of the esophagus or advanced/metastatic Siewert type 1 adenocarcinoma of the EGJ of at least 18 years of age will be enrolled in this trial.

Immune-related AEs	Toxicity grade or conditions (CTCAE v4.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
All other immune-related AEs	Intolerable/ persistent Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other cause
	Grade 3	Withhold or discontinue based on the type of event. Events that require discontinuation include and not limited to: Guillain-Barré Syndrome, encephalitis		
	Grade 4 or recurrent Grade 3	Permanently discontinue		

Abbreviations: AE=adverse event, ALT=alanine aminotransferase, AST=aspartate aminotransferase, CTCAE=Common Terminology Criteria for Adverse Events, irAE=immune-related adverse event, IV=intravenous, T1DM= Type 1 diabetes mellitus

NOTES:

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

5.2.2.2 Placebo

Placebo will be normal saline solution prepared by the local pharmacist. Placebo will be dosed and administered by blinded qualified trial site personnel in the same manner as the investigational product (pembrolizumab).

5.2.2.3 Cisplatin

Cisplatin 80 mg/m^2 will be administered as a 60- or 120-minute IV infusion (or per site's standard practice) Q3W on Day 1 of each treatment cycle after all procedures and assessments are completed according to Section 6.0 – Trial Flow Chart and after pembrolizumab/placebo administration. Duration of cisplatin treatment will be capped at 6 doses. Treatment with cisplatin may follow 1 to 2 days after pembrolizumab/placebo (eg, Day 2 or Day 3) as needed per local standard of care.

5.2.2.4 5-fluorouracil

5-fluorouracil will be administered as a continuous IV infusion of 800 mg/m^2/day on each of Days 1 to 5 Q3W or per local standard for 5-FU administration duration as long as total dose of 4000 mg/m^2 per 3-week cycle is followed (eg, 1000 mg/m^2/day on Days 1 to 4 Q3W is also acceptable). 5-FU will be administered after completion of all procedures and assessments according to Section 6.0 – Trial Flow Chart and after pembrolizumab/placebo administration. Treatment with 5-FU may follow 1 to 2 days after pembrolizumab/placebo (eg, Day 2 or Day 3) as needed per local standard of care. Duration of 5-FU treatment will not exceed 35 cycles.

Investigators are advised to counsel subjects assigned to receive 5-FU about risk of photosensitivity and to take sun protection measures accordingly.

5.2.3 Trial Blinding

A double-blinding technique will be used. Pembrolizumab and placebo will be prepared and/or dispensed in a blinded fashion by an unblinded pharmacist or qualified trial site personnel. The subject and the investigator who is involved in the treatment or clinical evaluation of the subjects are unaware of the group assignments.

Pembrolizumab or placebo treatment is blinded to the subject, study site personnel, and Sponsor personnel.

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

5.3 Randomization

Treatment randomization will occur centrally using an interactive voice response system / integrated web response system (IVRS/IWRS). There are 2 treatment arms. Subjects will be assigned randomly in a 1:1 ratio to pembrolizumab + cisplatin + 5-FU (Arm 1) or placebo + cisplatin + 5-FU (Arm 2).

Trial Period	Screening Phase	Treatment Cycles								End of Treatment	Post-treatment		
Treatment Cycle/Title	**Screening (Visit 1)**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8 and Beyond**	**Discon**	**Safety Follow-up**	**Follow-Up Visits**	**Survival Follow-Up[a]**
										At time of Discon	**30 Days post Last Dose**	**Every 9 Weeks Post-discon**	**Every 12 Weeks**
Scheduling Window (Days)[b]	**-28 to -1**		**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 7**	**± 7**	**± 7**
Blood for Plasma Biomarker Analyses[o]		X	X			X				X			
Blood for Serum Biomarker Analyses[o]		X	X			X				X			
Tumor Tissue Collection													
Newly Obtained or Archival Tumor Tissue	X[p]												
Efficacy Measurements													
Tumor Imaging	X[q]	<---------- X (every 9 weeks)[r] ---------->								X[s]		X	

a. In subjects that experience site-assessed PD or start a new anticancer therapy, contact should be made (eg, by telephone) approximately every 12 weeks to assess for survival status. Updated survival status may be requested by the Sponsor at any time during the course of the study. Upon Sponsor notification, all subjects who do not/will not have a scheduled study visit or study contact during the Sponsor defined time period will be contacted for their survival status (excluding subjects that have a death event previously recorded).
b. Cycle 1 treatment must be given within 3 days of allocation. The window for each visit is ± 3 days unless otherwise noted.
c. SAEs will be followed through 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier.
d. Refer to local regulations or local standard of practice for patient management regarding 5-FU and cisplatin treatment (eg, requirements for baseline and periodic audiograms for cisplatin).
e. Height will be measured at Visit 1 only.
f. ECOG performance status and laboratory tests for screening are to be performed within 14 days prior to the first dose of trial treatment.
g. See Section 7.1.2.6.2 – Electronic Patient-reported Outcomes for details regarding administration of PROs. All PROs are to be performed at Cycles 1 to 9. After Cycle 9 (Week 24), PROs are to be performed every 3 cycles (eg, Week 33, Week 42, Week 51). PROs are to be performed for up to 1 year or End of Treatment, whichever comes first, at time of discontinuation, and at the 30-day post-treatment discontinuation follow-up visit. A visit window of ± 7 days will apply to PRO visit assessments.
h. Pembrolizumab or placebo infusion is administered first, followed by the cisplatin and 5-FU infusions. Treatment with cisplatin and/or 5-FU may follow 1 to 2 days after pembrolizumab/placebo (eg, Day 2 or Day 3) as needed per local standard of care.
i. Pembrolizumab/placebo should be administered on Day 1 of each 3-week cycle after all procedures/assessments have been completed. Pembrolizumab 200-mg fixed dose or placebo should be administered as a 30-minute IV infusion Q3W. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. Given the variability of infusion pumps from site to site; however, a window of -5 minutes and +10 minutes is permitted (ie, infusion time between 25 and 40 minutes). Pembrolizumab/placebo treatment is discontinued after completion of 35 administrations (approximately 2 years).
j. Cisplatin will be capped at total of 6 doses; cisplatin dosing may occur after cycle 6 if cisplatin was withheld for one or more cycles during cycles 2 to 6.

initiation per local site assessment. This exception does not include carcinomatous meningitis, as subjects with carcinomatous meningitis are excluded regardless of clinical stability.

7.1.2.5.2 Tumor Imaging During the Trial

The first on-trial imaging assessment should be performed at 9 weeks (63 days ± 7 days) from the date of randomization. Subsequent tumor imaging should be performed every 9 weeks (63 days ± 7 days) or more frequently if clinically indicated. Imaging timing should follow calendar days and should not be adjusted for delays in cycle starts. Imaging should continue to be performed until PD is verified by the central imaging vendor (unless the site principal investigator elects to continue treatment and follow irRECIST), the start of new anticancer treatment, withdrawal of consent, or death, whichever occurs first. All supplemental imaging must be submitted to the central imaging vendor.

Per RECIST 1.1, partial response (PR) and CR should be confirmed by a repeat tumor imaging assessment obtained 4 weeks or longer from the date the response was first documented. The tumor imaging performed to confirm a response may be performed, at the earliest, 4 weeks after the first indication of a response, or at the next scheduled scan [i.e., 9 weeks later (63 days ± 7 days)], whichever is clinically indicated. Subjects will then return to regular scheduled imaging every 9 weeks (63 days ± 7 days), starting with the next scheduled imaging time point. Subjects who obtain a confirmation scan do not need to undergo the next scheduled tumor imaging if it is less than 4 weeks later; tumor imaging may resume at the subsequent scheduled imaging time point.

Per irRECIST, PD should be confirmed by the site at least 4 weeks after central verification of site-assessed first radiologic evidence of PD in clinically stable subjects. Subjects who have unconfirmed PD may continue on treatment at the discretion of the site investigator until progression is confirmed by the site as long as they have met the conditions detailed in Section 7.1.2.5.5 – irRECIST Assessment of Disease. Subjects who obtain a confirmation scan do not need to undergo the next scheduled tumor imaging if it is less than 4 weeks later; tumor imaging may resume at the subsequent scheduled imaging time point if clinically stable. Subjects who have confirmed PD, as assessed by the site, will discontinue trial treatment. Exceptions are detailed in Section 7.1.2.5.5 – irRECIST Assessment of Disease.

7.1.2.5.3 End of Treatment and Follow-up Tumor Imaging

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

In subjects who discontinue trial treatment without documented PD, every effort should be made to continue monitoring their disease status by tumor imaging using the same imaging schedule used while on treatment [every 9 weeks (63 days ± 7 days)] to monitor disease status until the start of a new anticancer treatment, PD, death, or the end of the trial, whichever occurs first.

function testing, which may be performed within 28 days prior to first dose. Pre-dose laboratory procedures can be conducted up to 72 hours prior to dosing.

Laboratory test results must be reviewed by the investigator or qualified designee and found to be acceptable prior to administration of each dose of trial treatment. Note, there may be instances when sites are unable to obtain the thyroid function testing results prior to scheduled dosing. After Cycle 1, review of thyroid function tests (T3 or FT3, FT4, and TSH) results after dosing is acceptable. Unresolved abnormal laboratory values 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 results are within the normal range.

7.1.3.2 Pregnancy Test

All women who are being considered for participation in the trial, and who are not surgically sterilized or postmenopausal, must be tested for pregnancy within 72 hours of randomization. If first dose of study treatment occurs > 72 hours after randomization, pregnancy test must be repeated to be within 72 hours of first dose of study treatment. Monthly pregnancy testing (serum and/or urine) should be conducted per local regulations where applicable. If a urine test is positive or not evaluable, a serum test will be required. Subjects must be excluded/discontinued from the trial in the event of a positive or borderline-positive test result.

7.1.3.3 HIV, Hepatitis B Virus, and Hepatitis C Virus Testing

Testing for HIV, hepatitis B virus, and hepatitis C virus will be conducted at screening only where required per local regulations using site standard operating procedures. Active hepatitis B is defined as a known positive hepatitis B surface antigen result. Active hepatitis C is defined by a known positive hepatitis C antibody result or known quantitative hepatitis C virus RNA results greater than the lower limits of detection of the assay.

7.1.3.4 Pharmacokinetic/Pharmacodynamic Evaluations

The accumulation of robust PK and ADA data has allowed for the adequate characterization the clinical pharmacology of pembrolizumab across indications, including for pembrolizumab monotherapy in esophageal cancer subjects and for subjects treated with pembrolizumab in combination with chemotherapy in other indications. Therefore, PK and ADA samples for this study will be limited to the first approximately 100 randomized subjects at Cycles 1, 2 and 4 only. Analysis will be performed only if required.

7.1.3.4.1 Blood Collection for Serum Pembrolizumab

Pre-dose PK samples will be collected at Cycles 1, 2 and 4 for the first approximately 100 randomized subjects. All pre-dose trough samples should be drawn within 24 hours before infusion of pembrolizumab/placebo. Sample collection, storage, and shipment instructions for serum samples will be provided in the Procedures Manual.

Note that no samples should be collected from subjects randomized after 31-Jan-2018, including all subjects from China.

Newly obtained tissue is preferred (no intervening treatment [local or systemic] involving the site of tissue biopsy once tissue biopsy is obtained and time of study enrollment). Formalin-fixed, paraffin-embedded block specimens are preferred to slides.

Detailed instructions for tissue collection, processing and shipment are provided in the Procedures Manual.

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 withdraws from participation in the trial, all applicable activities scheduled for the end of treatment visit should be performed at the time of withdrawal. Any adverse events which are present at the time of withdrawal should be followed in accordance with the safety requirements outlined in Section 7.2 - Assessing and Recording Adverse Events. After discontinuing treatment following assessment of CR or 35 administrations (approximately 2 years) of treatment, these subjects should return to the site for a Safety Follow-up Visit (described in Section 7.1.6.3.1 – Safety Follow-up Visit) and then proceed to the Follow-up Period of the study (described in Section 7.1.6.3.2 – Follow-up Visits).

7.1.4.1.1 Withdrawal From Future Biomedical Research

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

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

Note that Future Biomedical Research is not applicable for China.

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

7.2.3 Immediate Reporting of Adverse Events to the Sponsor

7.2.3.1 Serious Adverse Events

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

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

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

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

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

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

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

Additionally, any serious adverse event, considered by an investigator who is a qualified physician to be related to the Sponsor's product that is brought to the attention of the investigator at any time following consent through the end of the specified safety follow-up

7.2.5 Sponsor Responsibility for Reporting Adverse Events

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

7.3 TRIAL GOVERNANCE AND OVERSIGHT

7.3.1 Scientific Advisory Committee

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

7.3.2 Executive Oversight Committee

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

7.3.3 Data Monitoring Committee

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

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

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

The DMC will monitor the trial at an appropriate frequency, as described in the detailed DMC charter. Treatment-level results of the IA will be provided by the unblinded statistician to the DMC. Key enrollment metrics and study data will also be monitored by the external unblinded statistician to inform the timing of the first PFS and OS analyses as needed. The DMC will serve as the primary reviewer of the results of the main PFS analysis and will make recommendations for discontinuation of the study or modification to an EOC of the Sponsor. If the DMC recommends modifications to the design of the protocol or

Key Secondary Endpoints/Hypotheses	1. Objective response rate (ORR) based on RECIST 1.1 as assessed by investigator in all subjects.
Statistical Methods for Key Efficacy Analyses	The primary hypotheses will be evaluated by comparing pembrolizumab + chemotherapy arm to placebo + chemotherapy arm on PFS and OS using a stratified Log-rank test. Estimation of the hazard ratio (HR) will be done 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. The tiers differ with respect to the analyses that will be performed. There are no Tier I events in this study. Tier 2 parameters will be assessed via point estimates with 95% CI 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 [34].
Interim Analyses	One efficacy interim analysis will be performed in this study. Results will be reviewed by an external Data Monitoring Committee. Details are provided in Section 8.7 – Interim Analyses.
	Interim Analysis (IA): • Timing: (1) Enrollment is complete with a minimum follow-up of 13 months and (2) ~460 investigator-assessed PFS events have been observed in ESCC and (3) ~391 deaths have occurred in ESCC • Primary purpose: Final PFS analysis and Interim OS analysis FA: • Timing: (1) A minimum follow-up of 9 months after IA and (2) ~233 deaths have occurred in ESCC with PD-L1 CPS ≥10 and (3) ~455 deaths have occurred in ESCC. • Primary purpose: Final OS analysis
Multiplicity	The overall Type I error is strongly controlled at 2.5% (1-sided), with 1.2% initially allocated to OS in ESCC with PD-L1 CPS ≥10, 1.1% to OS in ESCC, 0 to OS in PD-L1 CPS ≥10, 0 to OS in all subjects, 0.2% to PFS in ESCC, 0 to PFS in PD-L1 CPS ≥10, and 0 to PFS in all subjects. Re-allocation of Type I error will use the graphical approach of Maurer and Bretz [35].
Sample Size and Power	The sample size is 749 subjects. As per preliminary baseline characteristics, the prevalence of ESCC with PD-L1 CPS ≥10 is 38%, PD-L1 CPS ≥10 is 51%, and ESCC is 73%. A total of ~233 deaths are expected in ESCC with PD-L1 CPS ≥10 at the OS final analysis. With 233 deaths, the study has ~85% power for detecting an HR of 0.65 at an initially assigned 0.012 (1-sided) significance level. A total of ~455 deaths are expected in ESCC at the OS final analysis. With 455 deaths, the study has ~88% power for detecting an HR of 0.72 at an initially assigned 0.011 (1-sided) significance level. A total of ~ 460 investigator-assessed PFS events are expected in ESCC at the interim analysis (IA). With ~460 PFS events, the study has ~82.8% power for detecting a HR of 0.7 at an initially assigned 0.002 (1-sided) significance level.

per RECIST 1.1 by investigator assessment, regardless of discontinuation of study drug or missed study visits. Death is always considered as a confirmed PD event. Subjects who do not experience a PFS event will be censored at the last disease assessment.

For the primary analysis, any subject who experiences an event (PD or death) immediately after 2 or more missed disease assessments will be censored at the last disease assessment prior to the missed visits. In addition, any subject who initiates new anti-cancer therapy will be censored at the last disease assessment prior to the initiation of new anti-cancer therapy. Subjects who do not start new anti-cancer therapy and who do not experience an event will be censored at the last disease assessment. If a subject meets multiple criteria for censoring, the censoring criterion that occurs earliest will be applied.

In order to evaluate the robustness of the PFS endpoint per RECIST 1.1 by investigator assessment, 2 sensitivity analyses with different sets of censoring rules will be performed. The first sensitivity analysis follows the intention-to-treat principle. That is, PDs/deaths are counted as events regardless of missed study visits or initiation of new anti-cancer therapy. The second sensitivity analysis considers discontinuation of treatment due to reasons other than complete response or initiation of new anticancer treatment, 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 the primary and sensitivity analyses are summarized in Table 11.

Table 13 Analysis Strategy for Key Efficacy Endpoints

Endpoint/Variable	Statistical Method	Analysis Population	Missing Data Approach
Primary Analyses			
PFS per RECIST 1.1 by investigator	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 subject's last known alive date
Key Secondary Analyses			
ORR per RECIST 1.1 by investigator	Testing and estimation: stratified Miettinen and Nurminen method	ITT	Subjects with missing data are considered nonresponders
Abbreviations: ITT = intent-to-treat; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors.			

8.6.2 Patient-reported Outcome Analyses: EORTC QLQ-C30 and QLQ-OES18

The PRO secondary objective is to compare the change from baseline on global health status quality of life scores in subjects treated with pembrolizumab in combination with chemotherapy versus placebo in combination with chemotherapy, based on the EORTC QLQ-C30 and 3 pre-specified disease-related symptom scores (dysphagia, reflux and pain) from the EORTC QLQ-OES18.

Additional PRO analyses will be described in the sSAP.

8.6.3 Statistical Methods for Safety Analyses

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

Tiered Approach

The analysis of safety results will follow a tiered approach (Table 14). The tiers differ with respect to the analyses that will be performed. "Tier 1" safety endpoints will be subject to inferential testing for statistical significance with p-values and 95% CI provided for between-group comparisons. Other safety parameters will be considered Tier 2 or Tier 3. Based on the safety data observed in historic pembrolizumab trials to date, there are no events of interest that warrant classification as Tier I events. Therefore, there are no events of interest that will be analyzed as Tier 1 safety endpoints in this study.

8.6.4 Summaries of Demographic and Baseline Characteristics

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 screened, randomized, the primary reasons for screening failure, and the primary reason for discontinuation will be displayed. Demographic variables (eg, age), baseline characteristics, primary and secondary diagnoses, and prior and concomitant therapies will be summarized by treatment either by descriptive statistics or categorical tables.

8.7 Interim Analyses

8.7.1 Safety Interim Analyses

As noted in Section 7.3.3 – Data Monitoring Committee, the DMC will be responsible for periodic interim safety reviews as specified in the DMC charter.

8.7.2 Efficacy Interim Analyses

One interim analysis is planned in addition to the final analysis for this study. For the interim and final analyses, all randomized subjects will be included. Results of the interim analysis will be reviewed by the DMC. Details of the boundaries for establishing statistical significance with regard to efficacy are discussed further in Section 8.8.

The analyses planned, endpoints evaluated, and drivers of timing are summarized in Table 15.

In the scenario that the OS hypothesis is rejected in ESCC with PD-L1 CPS ≥10 but is not rejected in ESCC, the OS test has approximately 89.9% power at FA to detect an HR of 0.65 at an overall α level of 0.006 (1-sided) in PD-L1 CPS ≥10. In the scenario that the OS hypothesis is rejected in ESCC but is not rejected in ESCC with PD-L1 CPS ≥10, the OS test has approximately 93.2% power at FA to detect an HR of 0.65 at an overall α level of 0.011 (1-sided) in PD-L1 CPS ≥10. In the scenario that the OS hypotheses in ESCC with PD-L1 CPS ≥10 and in ESCC are both rejected, the OS test has approximately 96.2% power at FA to detect an HR of 0.65 at an overall α level of 0.023 (1-sided) in PD-L1 CPS ≥10. In the scenario that OS hypotheses in ESCC with PD-L1 CPS ≥10, in ESCC, and in PD-L1 CPS ≥10 are all rejected, the OS test has approximately 94.2% power at FA to detect an HR of 0.75 at an overall α level of 0.023 (1-sided) in all subjects. In the scenario that OS hypotheses in all populations and all PFS null hypotheses are rejected, the OS test has approximately 94.6% power at FA to detect an HR of 0.75 at an overall α level of 0.025 (1-sided) in all subjects.

Based on 749 subjects with at least 10 months of follow-up, the power of the ORR testing at the allocated α=0.025 is approximately 98.7% to detect a 15-percentage point difference between an underlying 35% response rate in the control arm and a 50% response rate in the experimental arm.

8.10 Subgroup Analyses

To determine whether the treatment effect is consistent across various subgroups, as applicable, the estimate of the between-group treatment effect (with a nominal 95% CI) for the primary endpoints in subjects with esophageal squamous cell carcinoma (ESCC) whose tumors are PD-L1 biomarker-positive (CPS ≥10), in subjects with ESCC, in subjects whose tumors are PD-L1 biomarker-positive (CPS ≥10) and in all subjects will be estimated and plotted within each category of the following classification variables:

- Stratification factor: geographic region (Asia versus Rest of World)
- Stratification factor: histology (adenocarcinoma versus squamous cell carcinoma)
- Stratification factor: ECOG performance scale (0 versus 1)
- Age category (<65 versus ≥65 years)
- Sex (female versus male)
- Disease status (locally advanced versus metastatic)

Country-specific population (eg, Chinese, Japanese, EU, etc.) may also be analyzed per local regulatory requirements.

8.11 Compliance (Medication Adherence)

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

Abbreviation/Term	Definition
KN	KEYNOTE
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
MSD	Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
MSI	microsatellite instability
NA or N/A	not applicable
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NSAID	nonsteroidal anti-inflammatory drug
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
OTC	over the counter
P	pulse
PBPK	physiologically based pharmacokinetic
PD	progressive disease
PD-1	programmed cell death-1
PD-L1	programmed cell death-ligand 1
PD-L2	programmed cell death-ligand 2
PDLC	predefined limit of change
PFS	progression-free survival
PIN	Personal Identification Number
PK	pharmacokinetic
PO	*per os* (orally)
PR	partial response
PRO	patient-reported outcomes
PT	prothrombin time
Q3W	every 3 weeks
Q4W	every 4 weeks
Q9W	every 9 weeks
QLQ-C30	Quality of Life Questionnaire C30
QLQ-OES18	Quality of Life Questionnaire Oesophageal module
RBC	red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors