Official Protocol Title:	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)
NCT number:	NCT03189719
Document Date:	17-Jun-2020

SPONSOR:

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
(hereafter referred to as the Sponsor or Merck)

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

TITLE:

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)

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DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Amendment 09 / Global	17-JUN-2020	Due to higher than expected discordance rate in assessment of progressive disease between BICR (blinded independent central review) and investigator and following input from the US regulatory agency on the statistical analyses plan, the protocol is amended as follows: (i) change in primary endpoint from PFS by BICR to investigator-assessed and (ii) elimination of one of the two planned efficacy interim analyses.
Amendment 08 / Global	03-JAN-2020	1. Based on results from the KN181 study, 3 primary objectives and corresponding hypotheses were added: OS in esophageal squamous cell carcinoma (ESCC) population; OS in ESCC whose tumors are PD-L1 biomarker-positive (CPS ≥10) population; and PFS in ESCC population. 2. Secondary objectives updated accordingly with respect to ORR and DOR endpoints in the ESCC and ESCC PD-L1 CPS ≥10 populations. Exploratory objectives were updated for PFS per irRECIST in the ESCC and ESCC PD-L1 CPS ≥10 populations. 3. Due to the short interval (~5 months) between the last subject enrolled in the Global Cohort (n=711) and in the China Extension Study (n=38), these 2 subject groups are merged into 1 "Global Study" for the primary analyses (N=749). 4. To include assessment of DOR, QoL (C30) and QoL (OES18) in all pre-specified populations. The statistical analyses plan is updated accordingly
Amendment 07 / Global	Not activated	N/A

Document	Date of Issue	Overall Rationale
Amendment 06 / France-specific	28-JAN-2019	Apply changes from Global Amendment 05 to France-specific Amendment 03.
Amendment 05 / Global	12-DEC-2018	To extend the enrollment period beyond the Global Cohort to achieve the required sample size of the China Cohort to investigate efficacy and safety in Chinese subjects.
Amendment 04 / China-specific	21-SEP-2018	Remove all sampling, analysis and objectives for exploratory biomarkers for subjects from China as these were not approved by HGRAC
Amendment 03 / France-specific	02-FEB-2018	Apply changes from Global Amendment 02 to France-specific Amendment 01.
Amendment 02 / Global	19-DEC-2017	Change primary biomarker from GEP to PD-L1; clarify 5-FU dosing; update statistical analysis plan; reduce PK/ADA sampling
Amendment 01 / France-specific	20-OCT-2017	To address French HA requests for monthly pregnancy tests and mandatory audiograms for cisplatin use
Original Protocol	14-MAR-2017	Not applicable

SUMMARY OF CHANGES

PRIMARY REASON(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
2.1; 3.1; 3.2; 4.2.3.1.1; 4.2.3.1.2; 8.1; 8.4.1.1; 8.4.1.2; 8.6.1; 8.6.1.1; 8.6.1.3; 8.6.1.4; 8.7.2; 8.8.1.1; 8.8.1.3; 8.9	Trial Design; Primary Objective(s) & Hypothesis(es); Secondary Objective(s) & Hypothesis(es); Primary Efficacy Endpoints; Secondary Efficacy Endpoints; Statistical Analysis Plan Summary; Primary Efficacy Endpoints; Progression-free Survival; Objective Response Rate; Statistical Methods for Efficacy Analyses; Duration of Response; Efficacy Interim Analyses; Progression-free Survival; Objective Response Rate; Sample Size and Power Calculations; List of Abbreviations	Changed the primary endpoint of PFS, and the secondary endpoints of ORR and DOR, from BICR (blinded independent central review) assessment to investigator-assessment. Deleted one of the two planned interim analyses. Timing and criteria for triggering the IA were updated. Power and the number of PFS events were adjusted based on updated timing of IA.	These changes were made due to higher than expected discordance rate in assessment of progressive disease between BICR and investigator, and elimination of one of the two interim analyses following input from the US regulatory agency.

ADDITIONAL CHANGE(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
4.2.3.5; 7.1.1.1.2; 12.2	Future Biomedical Research Consent and Collection of Specimens for Future Biomedical Research Collection and Management of Specimens for Future Biomedical Research	Deleted “sub-trial”.	Future Biomedical Research (FBR) does not meet definition of a sub-trial per EU CTR and therefore, text was updated to make clear that FBR is not intended to be a sub-trial.
8.6.1.1; 8.6.1.3; 8.6.1.4	Progression-free Survival, Objective Response Rate, Duration of Response	Added that sensitivity analyses will be conducted for PFS, ORR, and DOR endpoints based on BICR.	Analyses based on BICR is replaced with investigator-assessment as the primary approach, and hence will be provided as sensitivity analyses.
8.6.3	Safety Analysis	Updated safety analysis methods with clarifications to the tiered approach for assessment of Tier 2 AEs.	This change is to align with analysis guidance for safety.

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
8.8.1	Multiplicity Control for Efficacy Analyses	Revised the alpha spending strategy to use the minimum of planned and actual events at the interim analysis. Added numbering of the hypotheses to Figure 3.	The minimum alpha spending strategy ensures that the actual spending will be no more aggressive than the planned, while at the same time ensuring that not all alpha is spent prior to final planned event counts. By using this more conservative spending early in the study, power can be retained to detect situations where the treatment effect may be delayed.
8.8.1.1; 8.8.1.2	Progression-free Survival, Overall Survival	Table 16 describing the efficacy boundaries and properties for PFS analyses was updated based on investigator assessment. Table 17 describing the efficacy boundaries and properties for OS analyses was updated.	The efficacy boundaries and properties for investigator-assessed PFS and OS analyses were updated based on 1 planned interim analysis and final analysis.

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
8.9	Sample Size and Power Calculations	Sample size and power calculations were updated using the "gsDesign" package in R instead of the EAST software.	To implement the minimum alpha spending strategy.
Minor editorial and formatting corrections were made throughout the document as clarification, to correct errors, and for consistency.			

No additional changes.

1.0 TRIAL SUMMARY

Abbreviated Title	First-line Esophageal Carcinoma Study with Chemo vs. Chemo + Pembrolizumab
Sponsor Product Identifiers	MK-3475 Pembrolizumab
Trial Phase	Phase III
Clinical Indication	First-line treatment of subjects with locally advanced unresectable or metastatic adenocarcinoma or squamous cell carcinoma of the esophagus or advanced/metastatic Siewert type 1 adenocarcinoma of the esophagogastric junction.
Trial Type	Interventional
Type of control	Placebo
Route of administration	Intravenous
Trial Blinding	Double-blind
Treatment Groups	Arm 1: Pembrolizumab + cisplatin + 5-fluorouracil Arm 2: Placebo + cisplatin + 5-fluorouracil
Number of trial subjects	The Global Cohort: approximately 700 subjects will be enrolled. The China Cohort will enroll approximately eligible 90 subjects in two enrollment periods: 1) The Global enrollment period: part of enrollment in the China Cohort will contribute towards enrollment in the Global Cohort until the Global Cohort completes enrollment of approximately 700 subjects. 2) The China extension enrollment period: remaining enrollment in China Cohort will occur in the China extension period until approximately 90 total subjects are enrolled in the China Cohort. Note: The sample size for China Cohort was updated to 106 from 90. The global cohort (n=711) and China extension study (n=38) will be merged into the Global Study population (N=749) for primary analyses. The study is fully enrolled.
Estimated duration of trial	The Global Cohort: The Sponsor estimates that the trial will require approximately 46 months from the time the first subject signs the informed consent until the last subject's last study-related phone call or visit. The China Cohort: The Sponsor estimates that the cohort will require approximately 32 months from the time the first subject signs in the informed consent until that last subject's last visit.

Duration of Participation	Each subject will participate in the trial from the time the subject signs the informed consent form through the final protocol-specified contact. After a screening phase of 28 days, each subject will be assigned to receive trial treatment until disease progression is confirmed by the site per immune-related Response Evaluation Criteria in Solid Tumors (irRECIST), unacceptable adverse event(s), intercurrent illness that prevents further administration of treatment, investigator's decision to discontinue the subject, noncompliance with trial treatment or procedure requirements or administrative reasons requiring cessation of treatment, or until the subject has received 35 administrations of pembrolizumab/placebo (approximately 2 years). After the end of treatment, each subject will be followed for the occurrence of adverse events and spontaneously reported pregnancy as described under Section 7.2 – Assessing and Recording Adverse Events. Subjects who discontinue for reasons other than disease progression will have post-treatment follow-up for disease status until disease progression is confirmed by the site per irRECIST, initiating a non-study cancer treatment, withdrawing consent, or becoming lost to follow-up. All subjects will be followed by telephone for overall survival until death, withdrawal of consent, or the end of the study.

Randomization Ratio	1:1

A list of abbreviations used in this document can be found in Section 12.5 – List of Abbreviations.

2.0 TRIAL DESIGN

2.1 Trial Design

This is a randomized, double-blind, placebo-controlled multi-site Phase III trial to evaluate the efficacy and safety of pembrolizumab in combination with cisplatin and 5-fluorouracil (5-FU) versus placebo in combination with cisplatin and 5-FU as first-line treatment in subjects with locally advanced unresectable or metastatic adenocarcinoma or squamous cell carcinoma of the esophagus or advanced/metastatic Siewert type 1 adenocarcinoma of the esophagogastric junction (EGJ).

Subjects will be required to have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and to provide a tumor sample adequate for central laboratory analysis of biomarkers that may be predictive of response to pembrolizumab.

The study will be enrolling into 2 cohorts: Global and China Cohorts. The enrollment period is divided into 2 periods: Global and China extension enrollment periods.

<u>The Global Cohort</u>

Approximately 700 eligible subjects will be randomized (1:1) to one of the following treatment arms, with allocation stratified by geographic region, histology, and ECOG performance score (see Section 5.4 – Stratification for more details).

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.

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.

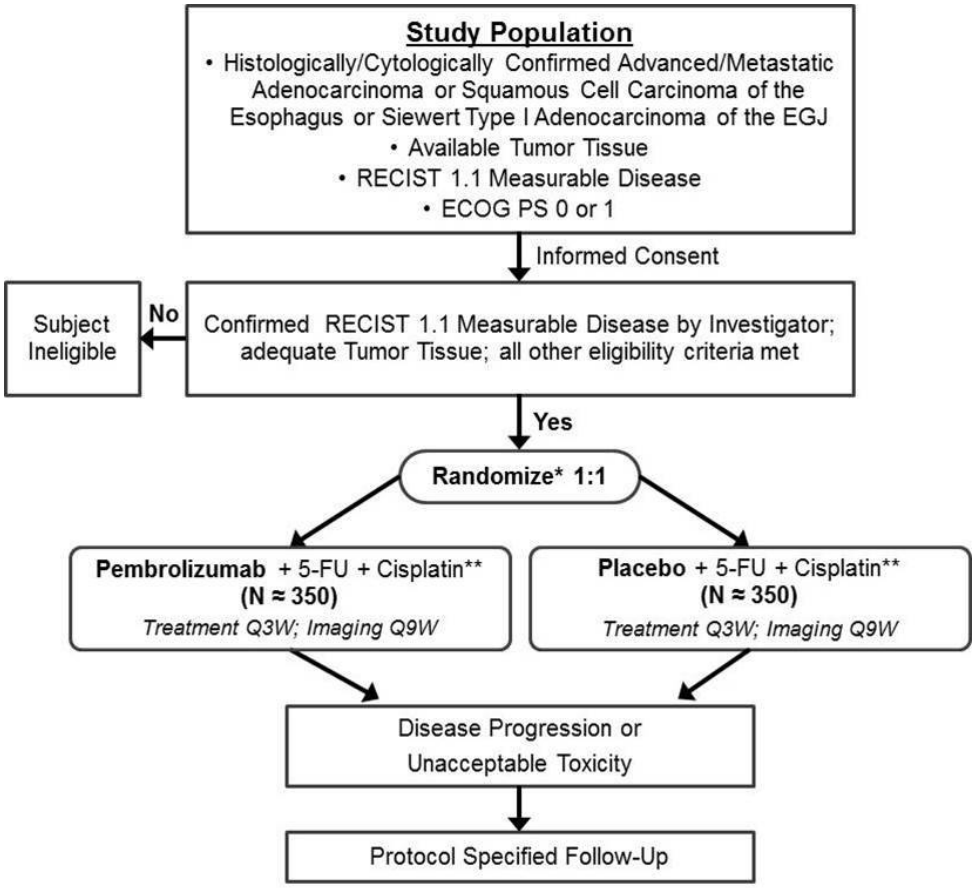
The China Cohort

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.



Abbreviations: EGJ=esophagogastric junction, 5-FU=5-fluorouracil, ECOG PS=Eastern Cooperative Oncology Group performance status, PS=Performance Score, RECIST=Response Evaluation Criteria in Solid Tumors, Q3W=every 3 weeks, Q9W=every 9 weeks

Figure 1 Trial Design Schematic

3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

The following objectives and hypotheses will be evaluated in 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. The chemotherapy regimen in each study arm comprises 5-FU and cisplatin.

The primary biomarker in this study is programmed cell death-ligand 1 (PD-L1) expression, and PD-L1 biomarker-positive is defined as combined positive score (CPS) ≥10 (see Section 4.2.3.4.1 – Biomarker Research for Primary Objectives for further details).

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.

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 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

Esophageal cancer is the sixth most common cause of cancer deaths in the world and is more prevalent in men than in women. In developing countries; however, esophageal cancer is endemic and is the fourth most common cause of cancer deaths. Globally, close to 480,000 cases occur annually, with 53% of these cases arising in China [15] [16]. In the US, in 2015, an estimated 15,980 esophageal cancers were expected to be diagnosed and it is estimated that 15,590 people would eventually die of their disease [17]. In Japan, esophageal cancer is the sixth leading cause of cancer deaths, and in 2008, there were 11,746 deaths from esophageal carcinoma, with male patients outnumbering female patients 6:1 [18]. The majority of patients are diagnosed with advanced/metastatic cancer and, in this setting, response to chemotherapeutic agents is poor. Given the high incidence and mortality worldwide and lack of good therapeutic options, esophageal cancer patients represent a high unmet need for drug development.

The geographical distribution of esophageal cancer varies widely, with a 60-fold difference between high- and low-prevalence regions. High-prevalence areas include Asia, Africa, and France, where squamous esophageal cancers predominate [19]. A dramatic shift in the histology and location of upper gastrointestinal (GI) tumors has occurred over the past decades. In Western countries, adenocarcinoma is the more predominant histology, with the most common site of esophageal cancer being in the lower third of the esophagus, which often involves the EGJ [20] [21] [22]. For the purpose of this study, the Siewert classification will be used for adenocarcinoma of the EGJ, and thus, type 1 patients (about 20% of the EGJ adenocarcinoma patients) will be eligible. Siewert type 1 tumors are adenocarcinomas of the lower esophagus with the center located within 1 to 5 centimeters above the anatomic EGJ. Type 2 and 3 Siewert adenocarcinomas of the EGJ are managed as gastric cancer patients, and therefore, would be eligible to participate in the first-line gastric trial, KN062. Adenocarcinoma has been gradually increasing in men of all ethnic backgrounds and also in women [23]. Squamous cell carcinoma seems to be more sensitive to chemotherapy, chemoradiation, and radiation therapy than adenocarcinoma, but the long-term outcome is similar for both histologies [24] [25], thus emphasizing the need for improved therapies in both histologies.

Phase III trials specifically designed for metastatic esophageal cancers have not been performed, and there is no definitive standard of care. Current guidelines for first-line treatment of advanced/metastatic esophageal cancer recommend combination treatment with platinum-based chemotherapy in combination with fluoropyrimidine as palliative therapy, with the combination of cisplatin and 5-FU being the most commonly used across regions. Docetaxel, paclitaxel, and irinotecan are included as options for second-line therapy for patients with locally advanced or metastatic disease. Other regimens included in the guidelines for patients with locally advanced or metastatic disease are derived from the gastric adenocarcinoma Phase III trials that have included patients with lower esophageal and/or EGJ cancer.

KN028 is a nonrandomized, multicohort, Phase 1b trial of pembrolizumab for PD-L1-positive advanced solid tumors that includes esophageal cancer patients. Key

eligibility criteria for this cohort include squamous cell carcinoma or adenocarcinoma of the esophagus or gastroesophageal junction, measurable disease, PD-L1 expression in ≥ 1% of cells in tumor nests or PD-L1-positive stromal bands determined centrally by IHC, failure of standard therapy, ECOG performance status 0 to 1, and no autoimmune disease. Pembrolizumab 10 mg/kg is administered every 2 weeks for up to 2 years or until confirmed PD. Of the 90 patients with esophageal cancer who have been screened, 37 (44.6%) have had PD-L1-positive tumors. Of the 23 patients treated between March and December 2014, 83% were men, and the median age was 65 years. Histology was squamous in 18 patients (78.3%) and adenocarcinoma in 5 patients (21.7%). Eighty-seven percent of patients received ≥ 2 prior therapies for metastatic disease; all patients received ≥ 1 platinum-based therapy. As of the data cutoff (20-Feb-2017), median follow-up was 7 months (range, 1 to 33 months). Treatment-related AEs occurred in nine patients (39%), most commonly decreased appetite, decreased lymphocyte count, generalized rash, and rash in two patients (9%) each. Grade 3 treatment-related AEs occurred in four patients (17%) and included decreased lymphocyte count in two patients (9%) and decreased appetite, liver disorder, and generalized rash in one patient (4%) each. There were no Grade 4 drug-related AEs, and no patients died due to a drug-related AE. Tumor shrinkage was seen in 52% of patients and ORR was 30% (95% confidence interval [CI], 13% to 53%) with seven responses confirmed partial responses (5 squamous [28%] and 2 adenocarcinoma [40%]). Stable disease was seen in 9% (N = 2) and PD in 59% (N = 13). Median time to initial response was 4 months (range, 2 to 8 months) and median duration of response was 15 months (range, 6 to 26+ months) for the patients in the esophageal cohort.

KN-180 is a Phase 2 open-label, interventional, single-arm study of pembrolizumab monotherapy in previously treated subjects with advanced/metastatic EAC or ESCC or advanced/metastatic Siewert type 1 adenocarcinoma of the EGJ. This open-label trial completed enrollment at 57 sites in 10 countries on 21-MAR-2017 with 121 subjects allocated to treatment. Patients had advanced, metastatic esophageal cancer that progressed after 2 or more lines of therapy and had evaluable tumor samples for biomarkers. Pembrolizumab 200 mg was administered intravenously every 3 weeks until disease progression, unacceptable toxic effects, or study withdrawal, for up to 2 years. As of 17-AUG-2018, of 121 enrolled patients (100 males and 21 females; median age, 65 years [range, 33-87 years]), 18 (14.9%) had undergone 3 or more prior therapies, 63 (52.1%) had ESCC, and 58 (47.9%) had tumors positive for programmed death ligand-1 (PD-L1), defined as a combined positive score of 10 or higher assessed by immunohistochemistry. Median duration of follow-up was 5.8 months (range, 0.2 to 27.8 months). Objective response rate was 9.9% (95% CI, 5.2%-16.7%) among all patients (12 of 121), and median duration of response was not reached (range, 2.1 to 25.1+ months). Objective response rate was 14.3% (95% CI, 6.7%-25.4%) among patients with ESCC (9 of 63), 5.2% (95% CI, 1.1%-14.4%) among patients with adenocarcinoma (3 of 58), 13.8% (95% CI, 6.1%-25.4%) among patients with PD-L1-positive tumors (8 of 58), and 6.3% (95% CI, 1.8%-15.5%) among patients with PD-L1-negative tumors (4 of 63). Overall, 15 patients (12.4%) had treatment-related Grade 3 to 5 adverse events. Seven patients (5.8%) discontinued treatment because of drug-related adverse events. There was 1 treatment-related death from pneumonitis.

KN-181, is a Phase 3, randomized, open-label study of single-agent pembrolizumab versus physicians' choice of single-agent docetaxel, paclitaxel, or irinotecan in subjects with

advanced/metastatic EAC and ESCC or advanced/metastatic Siewert type 1 adenocarcinoma of the EGJ that have progressed after first-line standard therapy. As of Nov 6, 2018, KN-181 has completed enrollment of 628 subjects. In PD-L1 CPS ≥10 subjects, there was significant clinical benefit with a median OS for pembrolizumab of 9.3 months versus 6.7 months for SOC. The OS rate of pembrolizumab versus SOC at 6 months was 63.6% and 54.1% respectively; and at 12 months was 42.1% and 20.4%, respectively. The ORR was 21.5% for pembrolizumab and 6.1% for SOC. In the ESCC subpopulation, pembrolizumab demonstrated a favorable OS benefit compared with SOC; the median OS for pembrolizumab was 8.2 months versus 7.1 months for SOC. The OS rate of pembrolizumab versus SOC at 6 months was 61.1% and 58.8% respectively; and at 12 months was 38.9% and 24.9%, respectively The ORR was 16.7% for pembrolizumab and 7.4% for SOC. In the overall study population, the median OS for pembrolizumab and SOC was 7.1 months. The ORR in all subjects was 13.1% for pembrolizumab and 6.7% for SOC. Confirmed complete response (CR) was reported in 9 subjects in the pembrolizumab arm and 2 subjects in the SOC arm. In an additional analysis in ESCC subjects whose tumors expressed PD-L1 CPS ≥10, there was significant clinical benefit with a median OS for pembrolizumab of 10.3 months versus 6.7 months for SOC. The OS rate of pembrolizumab versus SOC at 6 months was 65.9% and 52.7% respectively; and at 12 months was 47.1% and 22.6%, respectively. The ORR was 22.4% for pembrolizumab and 7.3% for SOC. These data underscore the superior OS with pembrolizumab monotherapy in a late line setting in esophageal cancer patients.

Thus, pembrolizumab has an acceptable safety profile and provides highly promising antitumor activity in patients with heavily pretreated, advanced esophageal carcinoma. The high unmet need, lack of efficacious approved therapies, and the above data with pembrolizumab strongly support further development of this drug in first-line patients with advanced/metastatic esophageal carcinoma, across both the squamous cell carcinoma and adenocarcinoma histologies.

4.2.2 Rationale for Dose Selection/Regimen/Modification

4.2.2.1 Justification for Treatment Regimen

There are currently no Phase III clinical trial data or approved therapy for first-line advanced/metastatic esophageal cancer, and no standard chemotherapy regimen has been established. Various palliative chemotherapy regimens have been investigated in esophageal cancer studies and have been shown to have at least some activity in the first-line setting, with responses ranging from 20% to 48% and 5-year survival rates of approximately 15%, with significant toxicity rates [26]. Current National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology (ESMO) guidelines recommend the combination of a fluoropyrimidine (5-FU or capecitabine) with platinum agents (cisplatin, oxaliplatin, or carboplatin), either alone or in combination with a third drug such as epirubicin or a taxane, as the most effective first-line treatment option. The most common regimen of 5-FU plus cisplatin has resulted in response rates of 13% to 35.9%, disease control rates of 57% to 63.9 %, median PFS of 3.6 months, and median survival of 5.5 to 6.7 months in reported Phase II trials [27] [28] [29] [30].

A Phase II study of first-line squamous cell carcinoma subjects treated with cisplatin (100 mg/m^2) plus 5-FU (1000 mg/m^2/day continuous Days 1 to 5), repeated every 3 weeks (Q3W), demonstrated a response rate of 35% for the combination arm compared with 19% for single-agent cisplatin. Median time to progression was 6.3 months and median OS was 7.7 months for the combination. Toxicity was more severe in the combination arm compared with cisplatin alone and included Grade 4 aplasia and septicemia, meningeal hemorrhage, cerebrovascular event, and ischemia of lower limb [27].

A Phase II study by the Japan Esophageal Oncology Group evaluated a first-line regimen of 20 mg/m^2 cisplatin plus 5-FU at 800 mg/m^2/day (continuous for Days 1 to 5), repeated every 4 weeks (Q4W), in subjects with advanced/metastatic squamous cell carcinoma. Overall response rate was 33.3%, with median response duration of 5.7 months and OS of 6.6 months. Hematological (including Grade 3 neutropenia and thrombocytopenia) and GI (nausea/vomiting, diarrhea, stomatitis) toxicities were the most common adverse reactions observed [28].

A German study of cisplatin (100 mg/m^2) plus 5-FU (1000 mg/m^2/day continuous Days 1 to 5), repeated Q4W, alone or in combination with cetuximab (400 mg/m^2) was performed in patients with advanced ESCC. Objective response rates were modestly higher in the cetuximab combination arm at 34% compared with 30% with cetuximab plus 5-FU alone, while confirmed response rates were lower for both, at 19% and 13%, respectively. Median PFS and OS were also longer in the cetuximab arm, at 5.9 and 9.5 months, respectively, compared with the cisplatin plus 5-FU arm at 3.6 and 5.5 months, respectively, although differences were not statistically different. The most common Grade 3 to 4 AEs were neutropenia, diarrhea, nausea, fatigue, and thrombocytopenia [29].

In the NCCN clinical practice guideline, a combination of 5-FU (750 to 1000mg/m^2/day continuous infusion, Days 1 to 4), and cisplatin (75 to 100 mg/m^2, 29 to 35 day cycle) is listed as a recommended regimen for the first-line setting (Esophageal NCCN and ESMO guidelines). While cisplatin doses of 100 mg/m^2 Q4W may be the preferred dose in Non-Asian clinical trials, doses of 60 to 80 mg/m^2 are more common for Asian patients. The proposed doses of 80 mg/m^2 cisplatin and 800 mg/m^2/day (Days 1 to 5) 5-FU in combination with pembrolizumab Q3W have been evaluated in a cohort of first-line subjects with gastric cancer (KN059), in which the combination was shown to have a manageable safety profile with no treatment-related discontinuations or deaths. The most common treatment-related AEs were nausea (52%), stomatitis (52%), decreased neutrophils (48%), and decreased appetite (44%) [31].

4.2.2.2 Rationale for Fixed Dose Pembrolizumab

The planned dose of pembrolizumab for this trial is 200 mg every 3 weeks (Q3W). Based on the totality of data generated in the pembrolizumab development program, 200 mg Q3W is the appropriate dose of pembrolizumab across all indications and regardless of tumor type. As outlined below, this dose is justified by:

- Clinical data from eight randomized studies demonstrating flat dose- and exposure-efficacy relationships from 2 mg/kg Q3W to 10 mg/kg every two weeks (Q2W)

- Clinical data showing meaningful improvement in benefit-risk including overall survival at 200 mg Q3W across multiple indications

- Pharmacology data showing full target saturation in both systemic circulation (inferred from pharmacokinetic [PK] data) and tumor (inferred from physiologically based pharmacokinetic [PBPK] analysis) at 200 mg Q3W

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

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

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

4.2.3 Rationale for Endpoints

4.2.3.1 Rationale for Efficacy Endpoints

4.2.3.1.1 Primary Efficacy Endpoints

Overall survival has been recognized as the gold standard for the demonstration of superiority of a new antineoplastic therapy in randomized clinical studies. Achieving superiority in OS; however, is likely to be complicated by the availability of multiple post-progression therapies being available to subjects as second-line treatment. Therefore,

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.

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.

5.1.2 Subject Inclusion Criteria

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

1. Be willing and able to provide written informed consent for the trial. The subject may also provide consent for Future Biomedical Research where approved by local authorities. However, the subject may participate in the trial without participating in Future Biomedical Research.
2. Be ≥ 18 years of age on the day of signing informed consent.
3. Have histologically or cytologically confirmed diagnosis of locally advanced unresectable or metastatic adenocarcinoma or squamous cell carcinoma of the esophagus or advanced/metastatic Siewert type 1 adenocarcinoma of the EGJ.
    a. Subjects with direct invasion into adjacent organs such as the aorta or trachea (T4b disease) should be closely evaluated for bleeding risk prior to enrollment and a Sponsor consultation before enrollment is required.
    b. Subjects with Siewert type 1 adenocarcinoma of the EGJ with known human epidermal growth factor receptor-2/neu (HER-2/neu)-positive tumors are not eligible. If HER-2/neu status is unknown, site should follow local standards for HER-2/neu testing.
4. Have measurable disease per RECIST 1.1 as determined by the local site investigator/radiology assessment. A lesion(s) situated in a previously irradiated area can be considered a target lesion(s) if progression has been demonstrated and the lesion(s) is considered measurable per RECIST 1.1 criteria.

    Note: The same image acquisition and processing parameters should be used throughout the study for a given subject.
5. Have an ECOG performance status of 0 to 1.
6. Provide either a newly obtained or archival tissue sample for PD-L1 by immunohistochemistry analysis. Newly obtained tissue is preferred. Formalin-fixed, paraffin-embedded (FFPE) block specimens are preferred to slides. Repeat samples will be required if none of the samples submitted (archival or newly obtained) is adequate. For purposes of this study, newly obtained tissue refers to tissue that was collected between the last line of therapy and the first dose of study medication.
    a. Tumor samples that meet the minimum acceptance criteria (as defined in the Procedures Manual) must be submitted to the PD-L1 testing lab prior to subject randomization in the study. If multiple tumor samples are submitted, at least one of the samples must be confirmed to be adequate by a pathologist (either local or from testing laboratory) prior to subject being enrolled.
    b. For subjects from whom newly obtained samples cannot be obtained (eg, inaccessible or subject safety concern), an archival specimen may be submitted.

c. If newly obtained tissue is provided and an archival tissue sample is available, it should also be provided to support evaluation of the clinical utility of PD-L1 analysis by immunohistochemistry in newly obtained vs. archival tissue samples. However, a subject will not be excluded from participating in the study if he/she has provided newly obtained tissue and an archival tissue sample is not available or is otherwise insufficient for analysis.

   Note: Tumor samples obtained from a lesion that received radiation therapy is not acceptable for biomarker analysis. If a subject has received prior radiation therapy, the subject is eligible if either a newly-obtained sample from a tumor lesion not previously irradiated or an archival sample that was obtained before receiving radiation therapy can be provided.

7. Female subjects of childbearing potential must have a negative urine or serum pregnancy test within 72 hours prior to randomization. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. If first dose is given > 72 hours post randomization, pregnancy test should be repeated within 72 hours of first dose.

8. Female subjects of childbearing potential must be willing to use an adequate method of contraception as outlined in Section 5.7.2 – Contraception, for the course of the study through 120 days after the last dose of study medication and up to 180 days after last dose of cisplatin.

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

9. Male subjects of childbearing potential must agree to use an adequate method of contraception as outlined in Section 5.7.2 – Contraception, starting with the first dose of study therapy through 120 days after the last dose of study medication and up to 180 days after last dose of cisplatin and refrain from donating sperm during this period.

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

10. Have adequate organ function as defined in Table 1. Specimens must be collected within 14 days prior to the start of study treatment.

Table 1 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count	≥ 1500/µL
Platelets	≥ 100 000/µL
Hemoglobin	≥ 9.0 g/dL or ≥ 5.6 mmol/L[a]
Renal	
Creatinine **OR** Measured or calculated[b] creatinine clearance (glomerular filtration rate can also be used in place of creatinine or creatinine clearance)	≤ 1.5 × ULN **OR** ≥ 60 mL/min for subject with creatinine levels > 1.5 × institutional ULN Cisplatin product label should be followed for acceptable creatinine clearance rates.
Hepatic	
Total bilirubin	≤ 1.5 × ULN **OR** direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 × ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 × ULN (≤ 5 × ULN for subjects with liver metastases)
Coagulation	
International normalized ratio (INR) **OR** prothrombin time (PT) Activated partial thromboplastin time (aPTT)	≤1.5 × ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants

Abbreviations: ALT (SGPT)=alanine aminotransferase (serum glutamic pyruvic transaminase); AST (SGOT)=aspartate aminotransferase (serum glutamic oxaloacetic transaminase); ULN=upper limit of normal

[a] Criteria must be met without erythropoietin dependency and without packed red blood cell transfusion within last 2 weeks.

[b] Creatinine clearance should be calculated per institutional standard.

Note: This table includes eligibility-defining laboratory value requirements for treatment; laboratory value requirements should be adapted according to local regulations and guidelines for the administration of specific chemotherapies.

5.1.3 Subject Exclusion Criteria

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

1. Has locally advanced esophageal carcinoma that is resectable or potentially curable with radiation therapy (as determined by local investigator).
2. Has had previous therapy for advanced/metastatic adenocarcinoma or squamous cell cancer of the esophagus or advanced/metastatic Siewert type 1 adenocarcinoma of the EGJ. Subjects may have received prior neoadjuvant or adjuvant therapy in consideration of following:
    a. Assessment of disease progression should be confirmed by CT scan. In certain situations, clinical evidence of disease progression such as any new or worsening malignant effusion (documented by ultrasound) and confirmation

by pathologic criteria (histology and/or cytology) may be acceptable for assessment.

b. Treatment with curative intent, including neoadjuvant/adjuvant treatment, given as chemotherapy or chemoradiotherapy, using standard of care agents or definitive chemoradiation, will count as a line of therapy if disease progression occurs during treatment or within 6 months of cessation of treatment.

c. Dose reduction and/or switching of one or more agents due to toxicity/intolerability as deemed clinically appropriate by the investigator will not constitute a new line of therapy.

3. Has had major surgery, open biopsy, or significant traumatic injury within 28 days prior to randomization, or anticipation of the need for major surgery during the course of study treatment.
4. Has a known additional malignancy that is progressing or requires active treatment. Exceptions include early-stage cancers (carcinoma in situ or Stage 1) treated with curative intent, basal cell carcinoma of the skin, squamous cell carcinoma of the skin, in situ cervical cancer, in situ breast cancer that has undergone potentially curative therapy, and in situ or intramucosal pharyngeal cancer.
5. Has known active central nervous system metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are radiologically stable (ie, without evidence of progression for at least 4 weeks by repeat imaging [note that the repeat imaging should be performed during study screening]), clinically stable and without requirement of steroid treatment for at least 14 days prior to first dose of trial treatment.
6. Has an active autoimmune disease that has required systemic treatment in past 2 years (ie, with use of disease-modifying agents, corticosteroids, or immunosuppressive drugs). Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment and is allowed. Brief (ie, < 7 days) use of systemic corticosteroids is allowed when use is considered standard of care by investigator.
7. Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment, or has a history of organ transplant, including allogeneic stem cell transplant.
8. Has a history of (non-infectious) pneumonitis that required steroids or has current pneumonitis.
9. Has an active infection requiring systemic therapy.
10. Has a history or current evidence of any condition (eg, known deficiency of the enzyme dihydropyrimidine dehydrogenase, hearing impairment, etc.), therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of

the subject to participate (eg, any contraindication to the use of cisplatin or 5-FU), in the opinion of the treating investigator.

Note: Sites in France will perform a systematic search for dihydropyrimidine dehydrogenase deficiency for subjects who are naive to 5-FU. This research should be performed before any administration of 5-FU.

11. Has known psychiatric or substance abuse disorder that would interfere with cooperation with the requirements of the trial.
12. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the screening visit through 120 days after the last dose of study medication and up to 180 days after last dose of cisplatin.
13. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent or with an agent directed to another co-inhibitory T-cell receptor (i.e., CTLA-4, OX-40, CD137) or has previously participated in a pembrolizumab (MK-3475) clinical trial.
14. Has severe hypersensitivity (≥ Grade 3) to any study treatment (pembrolizumab, cisplatin, or 5-FU) and/or any of its excipients.
15. Has a known history of active tuberculosis (TB; Mycobacterium tuberculosis).
16. Has a known history of human immunodeficiency virus (HIV) infection. No HIV testing is required unless mandated by local health authority.
17. Has known history of or is positive for hepatitis B (hepatitis B surface antigen reactive) or hepatitis C (hepatitis C virus RNA or hepatitis C antibody is detected). No hepatitis testing is required unless mandated by local health authority.
18. Is currently participating in or has participated in a study of an investigational agent or has used an investigational device within 4 weeks prior to the first dose of trial treatment.

    Note: Subjects who have entered the follow-up phase of an investigational trial may participate as long as it has been 4 weeks after the last dose of the previous investigational agent.
19. Has received a live vaccine within 30 days prior to the first dose of trial drug. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, Bacillus Calmette–Guérin, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed.
20. Has had radiotherapy within 14 days of randomization. Subjects who received radiotherapy >14 days prior to randomization must have completely recovered from any radiotherapy-related AEs/toxicities.

    Note: Subjects with ≤ Grade 2 neuropathy or ≤ Grade 2 alopecia are an exception to this criterion and may qualify for the study.

Note: See Appendix 12.6.1 France-specific Requirements for additional exclusion criterion related to French subjects and their eligibility to receive cisplatin.

5.2 Trial Treatment(s)

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

Table 2 Trial Treatments

Drug	Dose/Potency	Dose Frequency	Route of Administration	Treatment Period	Use
Pembrolizumab	200 mg	Q3W	IV infusion	Day 1 of each cycle	Experimental
Normal saline	NA	Q3W	IV infusion	Day 1 of each cycle	Placebo
Cisplatin[a]	80 mg/m^2	Q3W	IV infusion	Day 1[b] of each cycle	Comparator regimen and combination agent
5-FU	800 mg/m^2/day × 5 days (4000 mg/m^2 total per cycle)	Q3W	IV infusion	Continuous Days 1[b] to 5 of each cycle[c]	Comparator regimen and combination agent

[a] Duration of cisplatin treatment will be capped at 6 doses, however treatment with 5-FU may continue per local standard.
[b] Administration of cisplatin and/or 5-FU may begin 1 to 2 days following pembrolizumab/placebo (eg, Day 2 or Day 3) as needed per local standard of care, with end day for 5-FU adjusted accordingly
[c] 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, NA=not applicable, Q3W=every 3 weeks

Trial treatment for Cycle 1 should begin within 3 days of randomization. However, every effort should be made to begin trial treatment on day of randomization.

All trial treatments will be administered on an outpatient basis. For 5-FU continuous infusion, use of a portable infusion pump is preferred; however, hospitalization is acceptable if that is the standard procedure for the local site.

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

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

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

5.2.1 Dose Selection/Modification

5.2.1.1 Dose Selection (Preparation)

The rationale for selection of dose of pembrolizumab to be used in this trial is provided in Section 4.0 – Background & Rationale. Details on preparation and administration of pembrolizumab are provided in the Pharmacy Manual.

Preparation of cisplatin and 5-FU should follow the local product label and administration should follow local standard procedures. The body surface area in m2 should be calculated per local guidance.

5.2.1.2 Dose Modification

If appropriate, the investigator may attribute each toxicity event to cisplatin, 5-FU, or pembrolizumab and use a stepwise dose reduction according to Table 3, Table 4, Table 5, Table 6, and Table 7. For individual subjects requiring a dose modification, treatment for each new cycle may be delayed if the scheduled off-drug periods are not adequate to allow for recovery to Grade ≤1 or the baseline status of the subject (with the exception of alopecia).

Pembrolizumab/placebo dose reductions are not permitted. Pembrolizumab/placebo treatment may be interrupted or discontinued due to toxicity (see Section 5.8.1 – Discontinuation of Treatment). If a dose reduction for toxicity occurs with any agent, the dose may not be re-escalated. Subjects can have a maximum of 2 dose modifications (if applicable) to each of the components of study therapy throughout the course of the study for toxicities. If a subject experiences several toxicities and there are conflicting recommendations, follow the most conservative dose adjustment recommended (i.e., dose reduction appropriate to the most severe toxicity). Subjects who require a third dose modification to any particular component will have that agent discontinued.

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

The CTCAE v4.0 must be used to grade the severity of AEs. All dose modifications should be based on the AE requiring the greatest dose modification. Dose modifications are detailed in Table 3, Table 4, Table 5, Table 6, and Table 7. Exceptional circumstances to following the dose modification tables below may be considered after consultation with the Sponsor.

Table 3 Dose Modifications for Trial Medications

	Dose level 0	**Dose level -1**	**Dose level -2**	**Dose level -3**
Cisplatin	80 mg/m^2	60 mg/m^2 (75% of Level 0)	40 mg/m^2 (50% of Level 0)	Discontinue
5-fluorouracil	4000 mg/m^2/cycle	3000 mg/m^2/cycle (75% of Level 0)	2000 mg/m^2/cycle (50% of Level 0)	Discontinue
Pembrolizumab/ placebo	200 mg fixed dose	Dose reductions are not permitted	Dose reductions are not permitted	Dose reductions are not permitted

If a toxicity is not otherwise specified, investigators should refer to the product label or local guidelines for cisplatin and 5-FU for dose adjustments.

5.2.1.2.1 Dose Modification and Toxicity Management Guidelines for Pembrolizumab/Placebo

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

Adverse events associated with pembrolizumab exposure may represent an immunologic etiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical trial data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids, and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, or skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab and administer corticosteroids. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab are provided in Table 4.

Table 4 Dose Modification and Toxicity Management Guidelines for Immune-related Adverse Events Associated with Pembrolizumab

General instructions:

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

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

Immune-related AEs	Toxicity grade or conditions (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		

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).

Dose Modification and Toxicity Management of Infusion Reactions Related to Pembrolizumab

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

Table 5 Pembrolizumab Infusion Reaction Dose Modification and Treatment Guidelines

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

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

Other Allowed Dose Interruption for Pembrolizumab

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

5.2.1.2.2 Dose Modification for Cisplatin and 5-fluorouracil

Refer to criteria for cisplatin and 5-FU dose modification included in Table 6 and Table 7 respectively.

Table 6 Dose Modification Guidelines for Cisplatin Drug-Related Adverse Events

Category	Toxicity	Hold Cisplatin Treatment for Grade	Timing for Restarting Cisplatin Treatment	Dose for Restarting Cisplatin Treatment	Discontinue Cisplatin
Hematologic[c]	Neutropenia	3[a]	Neutrophil count resolves to > 1,000/mm^3	No Reduction (consider G-CSF)	Toxicity does not resolve within 4 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 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 weeks of last infusion or if > 2 dose level reductions exceeded
		4[a]	NA	Discontinue	Permanently discontinue cisplatin
	Thrombo-cytopenia	3 or 4[a]	Platelet count resolves to > 75,000/mm^3 or baseline	Reduce by 1 DL	Toxicity does not resolve within 4 weeks of last infusion or if > 2 dose level reductions exceeded
Non-hematologic	Creatinine increased	2	Toxicity resolves to Grade 0 or 1	Reduce by 1 DL	Toxicity does not resolve within 4 weeks of last infusion or if > 2 dose level reductions exceeded
		3 or 4[a]	Toxicity resolves to Grade 0 or 1	Reduce by 1 DL	Toxicity does not resolve within 4 weeks of last infusion or if > 2 dose level reductions exceeded
	Sensory neuropathy	3 or 4[a]	Toxicity resolves to Grade 0 or 1	Reduce by 1 DL	Toxicity does not resolve within 4 weeks of last infusion or if > 2 dose level reductions exceeded
	Ototoxicity[d]	1 or 2[b]	Toxicity resolves to Grade 0 or 1	Reduce by 1 DL	Toxicity does not resolve within 4 weeks of last infusion or if >2 dose level reductions exceeded
		3 or 4	NA	Discontinue	Permanently discontinue cisplatin
	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 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 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.

[d] Cisplatin is known to cause high frequency hearing loss. Follow local product label and institutional guidelines. If Grade 1 or 2 hearing loss occurs, the risk of additional hearing loss versus the potential benefit of continuing cisplatin chemotherapy should be made. Grade 3 and 4 hearing loss is an indication to discontinue cisplatin.

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

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.

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).

5.4 Stratification

Treatment randomization will be stratified according to the following factors:

1. Geographic region (Asia versus Rest of World)
2. Histology (adenocarcinoma versus squamous cell carcinoma)
3. ECOG performance status (0 versus 1)

5.5 Concomitant Medications/Vaccinations (Allowed & Prohibited)

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

5.5.1 Acceptable Concomitant Medications

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

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

5.5.2 Prohibited Concomitant Medication

Subjects are prohibited from receiving the following therapies during screening to the end of treatment of this trial:

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab

- Radiation therapy

  Note: radiation therapy to a symptomatic solitary lesion or to the brain may be allowed following consultation with Sponsor.

- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, Bacillus Calmette–Guérin, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed

- Systemic glucocorticoids for any purpose other than to modulate symptoms from an AE that is suspected to have an immunologic etiology or for cisplatin or 5-FU supportive care. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.

- Brivudine, sorivudine analogues, and other inhibitors of the enzyme dihydropyrimidine dehydrogenase should not be administered with 5-FU therapy.

Subjects who, in the assessment of the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the trial. Subjects may receive other medications that the investigator deems to be medically necessary.

5.5.3 Concomitant Medications to Be Used with Caution

- Cimetidine, metronidazole, and interferons may increase levels of 5-FU.
- Phenytoin should not be started with cisplatin therapy. Follow label and local guidelines for usage and dose adjustments.
- Subjects who are taking phenytoin in conjunction with 5-FU should be examined regularly due to a potential elevation in phenytoin plasma levels.
- Hepatotoxic effects (i.e., rise in alkaline phosphatase, transaminase, or bilirubin levels) are commonly observed under the treatment with 5-FU and levamisole.
- For 5-FU and cisplatin, refer to the product labels or local standards of care for further information regarding concomitant medications to be used with caution.

5.6 Rescue Medications & Supportive Care

5.6.1 Supportive Care Guidelines for Pembrolizumab

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined along with the dose modification guidelines in Table 4 of Section 5.2.1.2.1. Where appropriate, these guidelines include the use of oral or IV treatment with corticosteroids as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary, as symptoms may worsen when the steroid dose is decreased.

For each disorder, attempts should be made to rule out other causes such as metastatic disease, bacterial infection, or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab.

Note: If after the evaluation of the event, it is determined not to be related to pembrolizumab, the investigator does not need to follow the treatment guidance. Refer to Table 4 in Section 5.2.1.2.1 – Dose Modification and Toxicity Management Guidelines for Pembrolizumab/Placebo for guidelines regarding dose modification and supportive care.

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event.

5.6.2 Supportive Care Guidelines for Cisplatin

Refer to the product label or local standards of care for additional cisplatin supportive measures.

5.6.3 Supportive Care Guidelines for 5-fluorouracil

Refer to the product label or local standards of care for 5-FU supportive measures.

5.7 Diet/Activity/Other Considerations

5.7.1 Diet

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

5.7.2 Contraception

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

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

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

- She had a hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy, or bilateral tubal ligation/occlusion, at least 6 weeks prior to screening.
- She has a congenital or an acquired condition that prevents childbearing.

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

- Practice abstinence from heterosexual activity

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

- Use (or have their partner use) acceptable contraception during heterosexual activity

  Note: Acceptable methods of contraception are‡:

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

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

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study, subjects of childbearing potential must adhere to the contraception requirement (described above) from the day of study medication initiation (or 14 days prior to the

initiation of study medication for oral contraception) throughout the study period up to 120 days after the last dose of study medication and up to 180 days after last dose of cisplatin. If there is any question that a subject of childbearing potential will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

5.7.3 Pregnancy

If a subject inadvertently becomes pregnant while on study treatment, the subject will be immediately discontinued from trial treatment. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the Sponsor without delay and within 24 hours if the outcome is a serious adverse experience (eg, death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor. If a male subject impregnates his female partner, the trial personnel at the site must be informed immediately and the pregnancy must be reported to the Sponsor and followed as described in Section 7.2 – Assessing and Recording Adverse Events.

5.7.4 Use in Nursing Women

Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, subjects who are breastfeeding are not eligible for enrollment. Specific additional information follows for individual agents used in this trial.

5.7.4.1 Pembrolizumab Use in Nursing Women

It is unknown whether pembrolizumab is excreted in human milk.

5.7.4.2 Cisplatin Use in Nursing Women

Cisplatin has been reported to be found in human milk; subjects receiving cisplatin should not breastfeed.

5.7.4.3 5-fluorouracil Use in Nursing Women

It is not known whether 5-FU is excreted in human milk. Because 5-FU inhibits DNA, RNA, and protein synthesis, mothers should not nurse while receiving this drug.

5.8 Subject Withdrawal/Discontinuation Criteria

5.8.1 Discontinuation of Treatment

Discontinuation of treatment does not represent withdrawal from the trial.

As certain data on clinical events beyond treatment discontinuation may be important to the study, they must be collected through the subject's last scheduled follow-up, even if the

subject has discontinued treatment. Therefore, all subjects who discontinue trial treatment prior to completion of the treatment will still continue to participate in the trial as specified in Section 6.0 – Trial Flow Chart and Section 7.1.6.3 – Post-Treatment Visits.

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

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

- The subject or subject's legally acceptable representative requests to discontinue treatment.
- Confirmed radiographic PD as outlined in Section 7.1.2.5 – Tumor Imaging and Assessment of Disease (exception if the Sponsor approves treatment continuation)
- Unacceptable adverse experiences as described in Section 7.2 – Assessing and Recording Adverse Events
- Any progression or recurrence of any malignancy, or any occurrence of another malignancy that requires active treatment
- Intercurrent illness other than another malignancy as noted above that prevents further administration of treatment
- Recurrent Grade 2 pneumonitis
- A confirmed positive serum pregnancy test
- Investigator decision to discontinue treatment
- Completion of 35 treatments (approximately 2 years) with pembrolizumab/placebo
    - Note: The number of treatments is calculated starting with the first dose
- Administrative reasons

Discontinuation of Trial Treatment after CR:

- Discontinuation of treatment may be considered for subjects who have attained a confirmed CR and have been treated for at least 8 cycles (at least 24 weeks), receiving at least 2 cycles of study treatment beyond the date when the initial CR was declared.

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

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

5.8.2 Withdrawal from the Trial

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

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

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

5.8.3 Lost to Follow-up

If a subject fails to return to the clinic for a required trial visit and/or if the site is unable to contact the subject, the following procedures are to be performed:

- The site must attempt to contact the subject and reschedule the missed visit. If the subject is contacted, the subject should be counseled on the importance of maintaining the protocol-specified visit schedule.
- The investigator or designee must make every effort to regain contact with the subject at each missed visit (eg, telephone calls and/or a certified letter to the subject's last known mailing address or locally equivalent methods). These contact attempts should be documented in the subject's medical record.
- Note: A subject is not considered lost to follow-up until the last scheduled visit for the individual subject. The missing data for the subject will be managed via the prespecified statistical data handling and analysis guidelines.

5.9 Subject Replacement Strategy

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

5.10 Beginning and End of the Trial

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

5.11 Clinical Criteria for Early Trial Termination

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

The clinical trial may be terminated early if the extent (incidence and/or severity) of emerging effects/clinical endpoints is such that the risk/benefit ratio to the trial population as a whole is unacceptable. The trial may also be terminated early at time of efficacy IA in case of positive OS based on decision of the DMC. In addition, further recruitment in the trial or at particular trial site(s) may be stopped due to insufficient compliance with the protocol, GCP and/or other applicable regulatory requirements, procedure-related problems, or the number of discontinuations for administrative reasons is too high.

6.0 TRIAL FLOW CHART

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**
Administrative Procedures													
Informed Consent	X												
Informed Consent for Future Biomedical Research (optional)	X												
Inclusion/Exclusion Criteria	X												
Subject Identification Card	X												
Demographics and Medical History	X												
Prior and Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	X		
Post-study Anti-cancer Therapy Status												X	X
Survival Status[a]		<----------										---------->	X
Clinical Procedures/Assessments													
Review Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X[c]	
Full Physical Examination[d]	X									X			
Directed Physical Examination[d]		X	X	X	X	X	X	X	X				
Height[e], Weight, and Vital Signs (T,P,RR,BP)	X	X	X	X	X	X	X	X	X	X			
12-Lead Electrocardiogram (Local)	X												
ECOG Performance Status	X[f]	X	X	X	X	X	X	X	X	X			
PROs (HRQoL Measures)[g]		X	X	X	X	X	X	X	X[g]	X	X		

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			

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.

k. 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. Subjects must be excluded/discontinued in the event of a positive test result.
l. Urinalysis and thyroid function tests to be performed every other cycle. CBC (hematology) and chemistry to be performed every cycle. After Cycle 1, pre-dose laboratory procedures can be conducted up to 72 hours prior to dosing.
m. Both PK and anti-pembrolizumab antibody samples: pre-dose (trough) PK and anti-pembrolizumab antibody samples will be collected within 24 hours before infusion at Cycles 1, 2 and 4 for the first approximately 100 randomized subjects. No samples should be collected for any subject randomized after 31-Jan-2018, including all subjects from China.
n. This sample should be drawn for planned analysis of the association between genetic variants in DNA and drug response. This sample will not be collected at the site if there is either a local law or regulation prohibiting collection, or if the IRB/IEC does not approve the collection of the sample for these purposes. If the sample is collected, leftover extracted DNA will be stored for future biomedical research if the subject signs the Future Biomedical Research (FBR) consent. If the planned genetic analysis is not approved, but FBR is approved and consent is given, this sample will be collected for the purpose of FBR. Note that this sample is not applicable for China.
o. Whole blood samples should be collected pre-dose on Day 1 of Cycle 1, Cycle 2, and Cycle 5, and again at treatment discontinuation. Leftover samples will be stored for FBR if the subject signs the FBR consent. Note that these samples are not applicable for China.
p. At screening, either a newly obtained tumor tissue specimen (no intervening treatment [local or systemic] involving the site of tissue biopsy once tissue biopsy is obtained and time of study enrollment; preferred option) or an archival tumor specimen is required prior to randomization. If submitting a newly obtained specimen, an archival tumor sample is also requested (where available) to assess the clinical utility of PD-L1 analysis in newly obtained versus archived tissue samples. Formalin-fixed, paraffin-embedded block specimens are preferred to slides.
q. Screening tumor imaging will be performed within 21 days prior to randomization. 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. For all subjects, already available imaging scans performed as part of routine clinical management are acceptable if they are of diagnostic quality and performed within the acceptable timeframe.
r. The first on-study imaging time point will be performed at 9 weeks (63 days ± 7 days) calculated from the date of allocation and will continue to be performed Q9W (63 days ± 7 days), or earlier if clinically indicated. Imaging timing should follow calendar days and should not be adjusted for delays in cycle starts.
s. In order to follow irRECIST criteria, if a subject is discontinued from study therapy prior to PD being confirmed at the site, then that subject should have tumor imaging performed at the time of treatment discontinuation. If previous tumor imaging was obtained within 4 weeks prior to the date of discontinuation, then additional tumor imaging at treatment discontinuation is not required.

Abbreviations: 5-FU=5-fluorouracil, aPTT=activated partial thromboplastin time, BP=blood pressure, CBC=complete blood count, DNA=deoxyribonucleic acid, ECI=event of clinical interest, ECOG=Eastern Cooperative Oncology Group, FBR=Future Biomedical Research, FT4=free thyroxine, HRQoL=health-related quality of life, IEC=Independent Ethics Committee, INR=international normalized ratio, IRB=Institutional Review Board, irRECIST=immune-related Response Evaluation Criteria in Solid Tumors, IV=intravenous, P=pulse, PD=progressive disease, PD-L1=programmed cell death-ligand 1, PK=pharmacokinetics, PRO=patient-reported outcome, PT=prothrombin time, Q3W=every 3 weeks, Q9W=every 9 weeks, RNA=ribonucleic acid, RR=respiratory rate, SAE=serious adverse event, T=temperature, T3=triiodothyronine, TSH=thyroid-stimulating hormone.

7.0 TRIAL PROCEDURES

7.1 Trial Procedures

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

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

7.1.1 Administrative Procedures

7.1.1.1 Informed Consent

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

7.1.1.1.1 General Informed Consent

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

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

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

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

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

7.1.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

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

Note that Future Biomedical Research is not applicable for China.

7.1.1.2 Inclusion/Exclusion Criteria

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

7.1.1.3 Subject Identification Card

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

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

7.1.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee. The medical history will collect all active conditions and any condition diagnosed within the prior 10 years that the investigator considers to be clinically significant. Details regarding the subject's esophageal cancer will be recorded separately and not listed as medical history.

7.1.1.5 Disease Details

The investigator or qualified designee will obtain prior and current details regarding the subject's esophageal cancer.

7.1.1.6 Prior and Concomitant Medications Review

7.1.1.6.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the subject within 28 days before starting the trial. Treatment for the subject's esophageal cancer will be recorded separately and not listed as a prior medication.

7.1.1.6.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the subject during the trial through the Safety Follow-up visit.

All medications related to reportable SAEs and ECIs should be recorded as defined in Section 7.2 – Assessing and Recording Adverse Events.

7.1.1.6.2.1 Subsequent Anti-Cancer Therapy Status

The investigator or qualified designee will review all new anticancer therapy initiated after the last dose of trial treatment. If a subject initiates a new anticancer therapy within 30 days after the last dose of trial treatment, the 30-day Safety Follow-up visit must occur before the first dose of the new therapy.

Once new anticancer therapy has been initiated, the subject will move into survival follow-up. Details regarding survival status follow-up are outlined in Section 7.1.6.3.3 – Survival Follow-up.

7.1.1.7 Assignment of Screening Number

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

7.1.1.8 Assignment of Treatment/Randomization Number

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

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

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

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

Administration of trial medications will be witnessed by the investigator and/or trial staff.

The total volume of trial medication infused will be compared with the total volume prepared to determine compliance with each dose administered. The instructions for preparing and administering pembrolizumab/placebo are provided in the Pharmacy Manual.

Preparation and administration of 5-FU and cisplatin should be completed per the approved product label or per institutional guidelines.

7.1.2 Clinical Procedures/Assessments

7.1.2.1 Adverse Event Monitoring

The investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs as specified in the Section 6 – Trial Flow Chart and more frequently if clinically indicated. Adverse events will be graded and recorded throughout the trial and during the follow-up period according to NCI CTCAE v4.0 (see Section 7.2.4 – Evaluating Adverse Events). Toxicities will be characterized in terms including seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

Refer to Section 7.2 – Assessing and Recording Adverse Events for detailed information regarding the assessment and recording of AEs.

7.1.2.2 Physical Exam

7.1.2.2.1 Full Physical Exam

The investigator or qualified designee will perform a complete physical exam during the Screening period. Clinically significant abnormal findings should be recorded as medical history. The time points for full physical exams are described in Section 6 – Trial Flow Chart. After the first dose of trial treatment, new clinically significant abnormal findings should be recorded as AEs.

A complete physical examination is a comprehensive inspection of a subject's general appearance, HEENT, neck, chest and lungs, cardiovascular system, abdomen, genitourinary system, musculoskeletal system, lymph nodes, extremities, and neurological system by reviewing history, palpation, percussion, and auscultation.

Refer to local regulations or local standard of practice for patient management regarding 5-FU and cisplatin treatment (eg, requirements for baseline audiograms for cisplatin).

7.1.2.2.2 Directed Physical Exam

For cycles that do not require a full physical examination as defined in Section 6.0 – Trial Flow Chart, the investigator or qualified designee will perform a directed physical examination as clinically indicated prior to the administration of the trial treatment. New clinically significant abnormal findings should be recorded as AEs.

Refer to local regulations or local standard of practice for patient management regarding 5-FU and cisplatin treatment (eg, requirements for periodic audiograms for cisplatin).

7.1.2.3 Vital Signs

Vital signs include temperature, pulse, respiratory rate, weight and blood pressure. The investigator or qualified designee will take vital signs at screening, prior to the administration of each dose of trial treatment, and at treatment discontinuation as specified in the Section 6 – Trial Flow Chart. Height will be measured at Visit 1 only.

7.1.2.4 12-Lead Electrocardiogram

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

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.

7.1.2.5.4 RECIST 1.1 Assessment of Disease

RECIST 1.1 will be used by the central imaging vendor as the primary measure for assessment of tumor response, date of PD, and as a basis for all protocol guidelines related to disease status (eg, discontinuation of trial therapy). Initial tumor imaging showing site-assessed PD should be submitted to the central imaging vendor immediately. The site will be notified if the central imaging vendor verifies PD using RECIST 1.1.

Figure 2 illustrates the imaging flow involving verification of PD for clinically stable subjects.

7.1.2.5.5 irRECIST Assessment of Disease

Immune-related RECIST is RECIST 1.1 adapted as described below to account for the unique tumor response seen with immunotherapeutic drugs. Immune-related RECIST will be used by the site investigator/local radiology reviewers to assess tumor response and progression, and make treatment decisions. This data will be collected in the clinical database.

When feasible, subjects should not be discontinued until progression is confirmed by the local site investigator/radiology assessment. This allowance to continue treatment despite initial radiologic PD takes into account the observation that some subjects can have a transient tumor flare in the first few months after the start of immunotherapy, and then experience subsequent disease response. Subjects that are deemed clinically unstable are not required to have repeat tumor imaging for confirmation of PD. Tumor flare includes any of the following scenarios:

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

In subjects who have shown initial evidence of radiological PD by RECIST 1.1 as verified by the central imaging vendor, it is at the discretion of the principal investigator whether to continue a subject on trial medication until repeat imaging is obtained (using irRECIST for subject management (see Table 8 and Figure 2). This clinical judgment decision by the site investigator should be based on the subject's overall clinical condition, including performance status, clinical symptoms, and laboratory data. Subjects may receive trial medication and the tumor assessment should be repeated ≥ 4 weeks later in order to confirm PD by irRECIST per site assessment. Clinical stability is defined as the following:

- Absence of symptoms and signs indicating clinically significant progression of disease, including worsening of laboratory values
- No decline in ECOG performance status
- Absence of rapid progression of disease
- Absence of progressive tumor at critical anatomical sites (eg, cord compression) requiring urgent alternative medical intervention)

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

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

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

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

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

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

- Target lesion sum of diameters remains ≥ 20% and at least 5 mm absolute increase compared to nadir
- Non-target disease resulting in initial PD is qualitatively worse
- New lesion resulting in initial PD is qualitatively worse
- Additional new lesion(s) since last evaluation
- Additional new non-target lesion progression since last evaluation

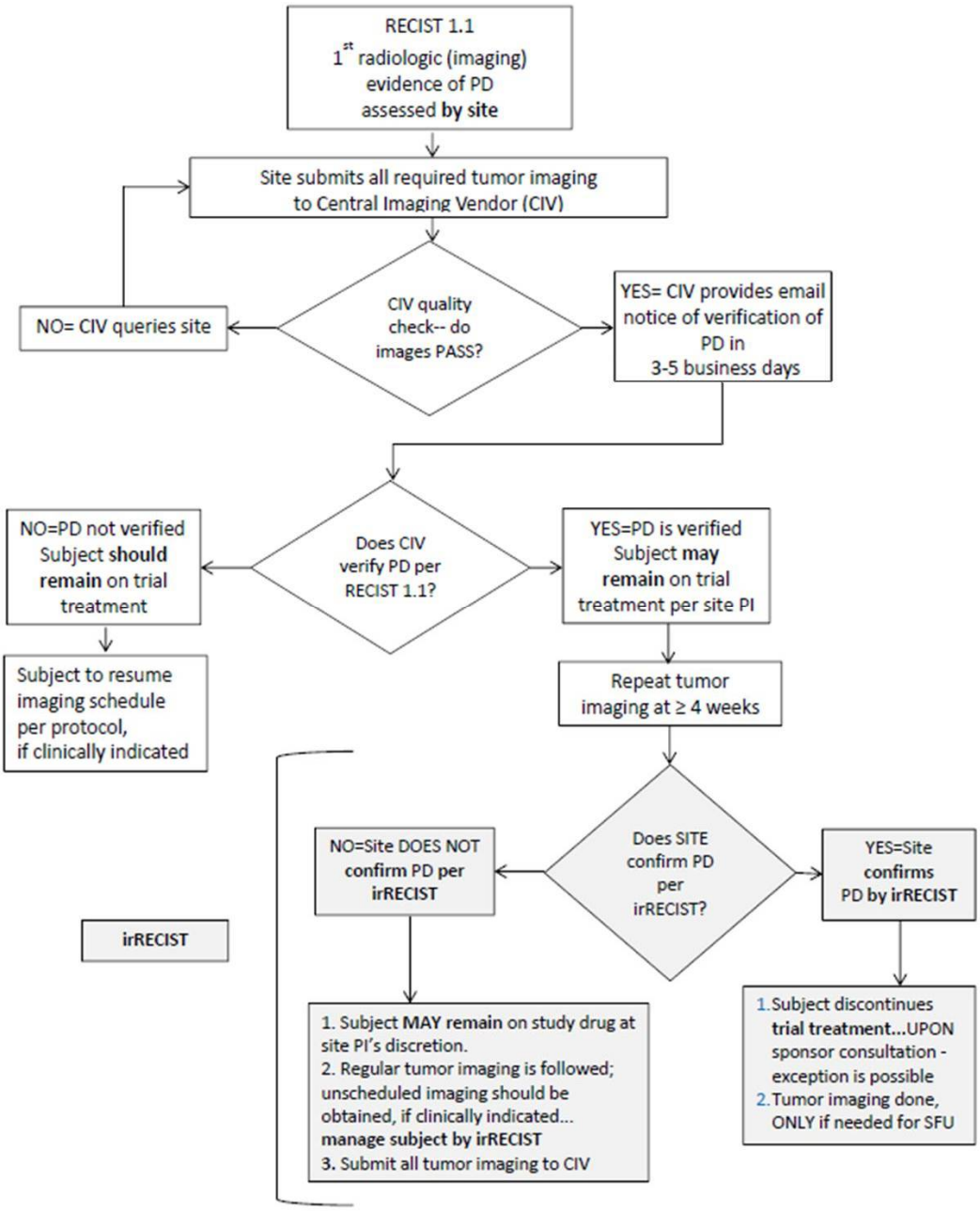
If repeat imaging confirms PD due to any of the scenarios listed above, subjects will be discontinued from trial therapy.

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

Additional details about irRECIST are provided in Merck TIP Sheet for RECIST 1.1 and irRECIST.

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

	Clinically Stable		**Clinically Unstable**	
	Imaging	**Treatment**	**Imaging**	**Treatment**
First radiologic evidence of PD by RECIST 1.1 which has been verified by the central imaging vendor	Repeat imaging at ≥ 4 weeks at site to confirm PD	May continue trial treatment at the local site investigator's discretion while awaiting confirmatory tumor imaging by site by irRECIST.	Repeat imaging at ≥ 4 weeks to confirm PD per investigator's discretion only	Discontinue treatment
Repeat tumor imaging confirms PD by irRECIST at the local site	No additional imaging required	Discontinue treatment (exception is possible upon consultation with Sponsor)	No additional imaging required	Not applicable
Repeat tumor imaging shows SD, PR or CR by irRECIST at the local site	Continue regularly scheduled imaging assessments	Continue trial treatment at the local site investigator's discretion	Continue regularly scheduled imaging assessments	May restart trial treatment if condition has improved and/or clinically stable per investigator's discretion. Next tumor image should occur according to the regular imaging schedule
CR=complete response, irRECIST=immune-related Response Evaluation Criteria in Solid Tumors, PD=progressive disease, PFS=progression-free survival, PR=partial response, SD=stable disease				



Abbreviations: CIV=central imaging vendor; PD=progressive disease; SFU=safety follow-up; RECIST= Response Evaluation Criteria in Solid Tumors; irRECIST=immune-related RECIST; PI=principle investigator

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

7.1.2.6 Performance and Quality of Life Assessments

7.1.2.6.1 Eastern Cooperative Oncology Group Performance Scale

The investigator or qualified designee will assess ECOG status (see Section 12.3 – ECOG Performance Status) at screening, prior to the administration of each dose of trial treatment, and at treatment discontinuation as specified in Section 6 – Trial Flow Chart.

7.1.2.6.2 Electronic Patient-reported Outcomes

The following health-related quality of life assessment tools will be administered by trained study site personnel and completed electronically by subjects. It is strongly recommended that electronic patient-reported outcomes (ePROs) are administered prior to drug administration, AE evaluation, and disease status notification; an exception to this recommendation may occur at the treatment discontinuation visit. Electronic patient-reported outcome will be administrated in the following order: the EuroQoL EQ-5D-5L first, followed by EORTC QLQ-C30, and lastly the EORTC QLQ-OES18 at the time points specified in Section 6 – Trial Flow Chart. If the subject does not complete a given ePRO assessment, the MISS_MODE form must be completed to capture the reason the assessment was not performed. A visit window of ± 7 days will apply to ePRO visit assessments.

If at the time of enrollment of a subject, the translated version of the EORTC QLQ-OES18 is not available for that language/country, and therefore cannot be completed by the subject at Cycle 1 Day 1, then the EORTC QLQ-OES18 will not be required for this subject at any point during the study. The other study patient-reported outcomes (PRO) measures must be completed as scheduled. NOTE: For some sites, the translated EORTC QLQ-OES18 might become available after study startup and should be administered to subjects at their time of enrollment; for some sites, the EORTC QLQ-OES18 translation might not be available for the entire duration of the study.

7.1.2.6.2.1 EuroQoL EQ-5D-5L

The EuroQoL EQ-5D-5L is a standardized instrument for use as a measure of health outcome and will provide data for use in economic models and analyses including developing health utilities or quality-adjusted life-years. The 5 health state dimensions in this instrument include the following: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension is rated on a 5-point scale from 1 (no problem) to 5 (extreme problem). The EuroQoL EQ-5D-5L also includes a graded (0 to 100) vertical visual analog scale on which the subject rates his or her general state of health at the time of the assessment. The EuroQoL EQ-5D-5L will always be completed electronically by subjects first, prior to completing any other ePRO.

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

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.

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.

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.

7.1.4.1.2 Lost to Follow-up

If a subject fails to return to the clinic for a required study visit and/or if the site is unable to contact the subject, the following procedures are to be performed:

- The site must attempt to contact the subject and reschedule the missed visit. If the subject is contacted, the subject should be counseled on the importance of maintaining the protocol-specified visit schedule.
- The investigator or designee must make every effort to regain contact with the subject at each missed visit (eg, phone calls and/or a certified letter to the subject's last known mailing address or locally equivalent methods). These contact attempts should be documented in the subject's medical record.

  Note: A subject is not considered lost to follow-up until the last scheduled visit for the individual subject. The amount of missing data for the subject will be managed via the pre-specified data handling and analysis guidelines.

7.1.4.2 Subject Blinding/Unblinding

STUDY TREATMENT IDENTIFICATION INFORMATION IS TO BE UNMASKED ONLY IF NECESSARY FOR THE WELFARE OF THE PARTICIPANT. EVERY EFFORT SHOULD BE MADE NOT TO UNBLIND THE PARTICIPANT UNLESS NECESSARY.

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

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

Additionally, the investigator must go into the IVRS system and perform the unblind in the IVRS system to update drug disposition. In the event that the emergency unblinding call center is not available for a given site in this trial, IVRS/IWRS should be used for emergency unblinding in the event that this is required for subject safety.

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

In the event that unblinding has occurred, the circumstances around the unblinding (e.g., date, reason and person performing the unblinding) must be documented promptly, and the

Sponsor Clinical Director notified as soon as possible. Once an emergency unblinding has taken place, the principal investigator, site personnel, and Sponsor personnel may be unblinded so that the appropriate follow-up medical care can be provided to the participant.

7.1.4.3 Calibration of Equipment

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

- Laboratory equipment – as required for inclusion labs and trial assessments
- Imaging equipment – as required for study objectives

See protocol-specified guidance in the Administrative Binder, Procedures Manual, and Site Imaging Manual.

7.1.5 Medical Resource Utilization and Health Economics

All-cause hospitalizations and emergency room visits must be reported in the eCRF, from the time of treatment allocation/randomization through 90 days following cessation of study treatment, or 30 days following cessation of study treatment, if the subject initiates new anticancer therapy, whichever is earlier.

7.1.6 Visit Requirements

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

7.1.6.1 Screening Visit

Within 28 days prior to treatment randomization, potential subjects will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5.1 – Entry Criteria. Visit requirements are outlined in the Section 6 – Trial Flow Chart. Screening procedures may be repeated.

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

- Laboratory tests are to be performed within 14 days prior to the first dose of trial treatment. Exceptions are thyroid function and hepatitis testing, which may be done up to 28 days prior to the first dose of trial treatment.
- Evaluation of ECOG is to be performed within 14 days prior to the first dose of trial treatment.

- For women of reproductive potential, a urine or serum pregnancy test will 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 the first dose of trial treatment. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required (performed by the local trial site laboratory).
- Initial tumor imaging at Screening must be performed within 21 days prior to the date of randomization.

Subjects may be not be rescreened after failing to meet the inclusion/exclusion criteria during the initial 28-day screening period.

7.1.6.2 Treatment Period Visits

Visit requirements are outlined in the Section 6 – Trial Flow Chart. Specific procedure related details are provided in Section 7.1 – Trial Procedures.

7.1.6.3 Post-Treatment Visits

7.1.6.3.1 Safety Follow-up Visit

The mandatory Safety Follow-up Visit should be conducted approximately 30 days after the last dose of trial treatment or before the initiation of a new anticancer treatment, whichever comes first.

7.1.6.3.2 Follow-up Visits

Subjects who discontinue trial treatment for a reason other than PD will move into the Follow-up Phase and should be assessed by radiologic evaluation every 9 weeks (63 days ± 7 days) to monitor disease status. Every effort should be made to collect information regarding disease status until the start of new anticancer therapy, PD, death, or end of trial. Information regarding post-trial anticancer treatment will be collected if new treatment is initiated.

7.1.6.3.3 Survival Follow-up

Subjects who experience confirmed PD or start a new anticancer therapy will move into the Survival Follow-up Phase and should be contacted by telephone approximately every 12 weeks (84 days ± 7 days) to assess for survival status until death, withdrawal of consent, or the end of the trial, whichever occurs first.

7.1.6.4 Survival Status

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

period will be contacted for their survival status (excluding subjects 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.

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

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.)	

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

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.

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.

8.2 Responsibility for Analyses/In-house Blinding

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

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

The investigators, other study site staff, and subjects will be blinded to subject-level biomarker status. Analysis or summaries generated by biomarker status will be limited and documented.

The study will be conducted as a double-blind, Phase III study under in-house blinding procedures. The official, final database will not be unblinded until medical/scientific review has been performed, protocol deviations have been identified, and data have been declared final and complete. In addition, the independent radiologist(s) will perform the central imaging review without knowledge of treatment group assignment. Additional details regarding trial blinding/unblinding including unblinding required for operational purposes (eg, unblinded pharmacist) are described in Section 5.2.3 – Trial Blinding.

The planned efficacy IA is described in Section 8.7 – Interim Analyses. Blinding to treatment assignment will be maintained at all investigational sites. Treatment-level results of the efficacy IA will be provided by an external unblinded statistician to the DMC (see Section 7.3.3 – Data Monitoring Committee).

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

8.3 Hypotheses/Estimation

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

8.4 Analysis Endpoints

8.4.1 Efficacy Endpoints

8.4.1.1 Primary Efficacy Endpoints

Progression-free Survival – RECIST 1.1 by investigator assessment

Progression-free survival is defined as the time from randomization to the first documented disease progression per RECIST 1.1 based on investigator assessment or death due to any cause, whichever occurs first. See Section 8.6.1.1 – Progression-free Survival for the definition of censoring.

Overall Survival

Overall survival is defined as the time from randomization to death due to any cause. Subjects without documented death at the time of 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

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

Situation	Primary Analysis	Sensitivity Analysis 1	Sensitivity Analysis 2
PD or death documented after ≤1 missed disease assessment, and before new anti-cancer therapy, if any	Progressed at date of documented PD or death	Progressed at date of documented PD or death	Progressed at date of documented PD or death
Death or progression after ≥2 consecutive missed disease assessments without further valid non-PD disease assessments, or after new anti-cancer therapy	Censored at last disease assessment prior to the earlier date of ≥2 consecutive missed disease assessment and new anti-cancer therapy, if any	Progressed at date of documented PD or death	Progressed at date of documented PD or death
No PD and no death; and new anticancer treatment is not initiated	Censored at last disease assessment	Censored at last disease assessment	Progressed at treatment discontinuation due to reasons other than complete response; otherwise censored at last disease assessment if still on study treatment or completed study treatment.
No PD and no death; new anticancer treatment is initiated	Censored at last disease assessment before new anticancer treatment	Censored at last disease assessment	Progressed at date of new anticancer treatment
Abbreviations: PD = progressive disease			

The proportional hazards assumption on PFS will be examined using both graphical and analytical methods if warranted. The log[-log] of the survival function versus time for PFS will be plotted for the comparison between the pembrolizumab + chemotherapy arm and the placebo + chemotherapy arm. If the curves are not parallel, indicating that hazards are not proportional, supportive analyses may be conducted to account for the possible non-proportional hazards effect associated with immunotherapies: for example, using Restricted Mean Survival Time method [36], parametric method [37], etc. Further details of sensitivity analyses will be described in the sSAP as needed.

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

8.6.1.2 Overall Survival

The non-parametric Kaplan-Meier method will be used to estimate the survival rates over time. The hypotheses of treatment difference in survival 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, the HR). The HR and its 95% CI from the stratified Cox model with a single treatment covariate will be reported. The stratification factors used for randomization will be applied to both the stratified log-rank test and the stratified Cox model.

Subjects in the placebo + chemotherapy arm are expected to discontinue treatment earlier compared with subjects in the pembrolizumab + chemotherapy arm and may switch to another anti PD-1 treatment following the verification of PD by the central imaging vendor. Exploratory analyses to adjust for the effect of crossover to other PD-1 therapies on OS may be performed based on recognized methods (eg, the Rank Preserving Structural Failure Time model proposed by Robins and Tsiatis [38], 2-stage model, etc., based on an examination of the appropriateness of the data to the assumptions required by the methods).

8.6.1.3 Objective Response Rate

Stratified Miettinen and Nurminen method [34] will be used for comparison of the ORR between the treatment arms. The difference in ORR and its 95% CI from the stratified Miettinen and Nurminen method with strata weighting by sample size will be reported. The stratification factors used for randomization will be applied to the analysis.

The ORR hypotheses will be tested according to the hypotheses-testing plan as described in Section 8.8 – Multiplicity.

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

8.6.1.4 Duration of Response

If sample size permits, DOR will be summarized descriptively using the non-parametric Kaplan-Meier method. Only the subset of subjects who achieved CR or PR will be included in this analysis.

Censoring rules for DOR are summarized in Table 12.

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.

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.

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.				

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.

Table 15 Summary of Interim and Final Analyses Strategy

Analyses	Key Endpoints	Timing	Estimated Time after First Subject Randomized	Primary Purpose of Analysis
IA	PFS in ESCC; PFS in PD-L1 CPS≥10; PFS in All subjects; OS in ESCC with PD-L1 CPS≥10; OS in ESCC; OS in PD-L1 CPS≥10; OS in All subjects	(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 At this time ~200 deaths are expected to have occurred in ESCC with PD-L1 CPS≥10 and ~ 267 deaths are expected to have occurred in PD-L1 CPS≥10	~35 months	• Final PFS analysis • Interim OS analysis
FA	OS in ESCC with PD-L1 CPS≥10; OS in PD-L1 CPS≥10; OS in ESCC; OS in All subjects	(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. At this time ~311 deaths are expected to have occurred in PD-L1 CPS≥10	~44 months	• Final OS analysis

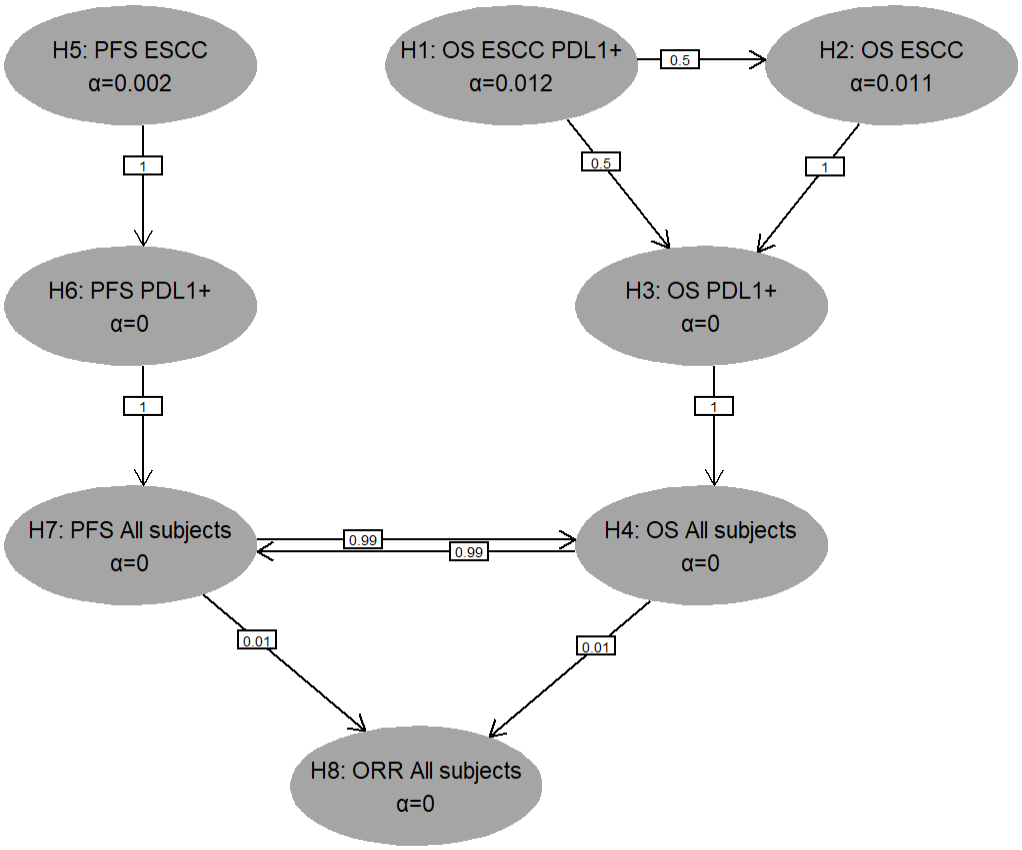
Abbreviations: FA = final analysis; IA = interim analysis; OS = overall survival; PFS = progression-free survival.

8.8 Multiplicity

8.8.1 Multiplicity Control for Efficacy Analyses

The study uses the graphical method of Maurer and Bretz [40] to provide strong multiplicity control for multiple hypotheses as well as interim analysis. According to this approach, study hypotheses may be tested more than once, and when a particular null hypothesis is rejected, the α allocated to that hypothesis can be reallocated to other hypothesis tests. Figure 3 shows the initial 1-sided α allocation for each hypothesis in the ellipse representing the hypothesis.

The weights for re-allocation from each hypothesis to the others are shown in the boxes on the lines connecting hypotheses.



Abbreviations: ORR = objective response rate; OS = overall survival; PFS = progression-free survival.

Figure 3 Multiplicity Diagram for Type I Error Control

8.8.1.1 Progression-free Survival

The study will test the PFS hypothesis once, at IA which will represent FA for PFS as assessed by the investigator. The initial α assigned to PFS in ESCC will be 0.002. If PFS hypothesis in ESCC subjects is rejected, the α will be reallocated to PFS in subjects with PD-L1 CPS ≥10. If PFS hypothesis in subjects with PD-L1 CPS ≥10 is also rejected, the α will be reallocated to PFS in all subjects. If all the OS null hypotheses are rejected, 0.99 of the initially allocated α i.e. 0.023 to OS hypotheses will be reallocated to test the PFS hypothesis in all subjects. Thus, if the PFS null hypotheses in the ESCC and the PDL1 CPS ≥10 populations are rejected and the OS hypothesis in all subjects is not rejected the PFS null hypothesis in all subjects may be tested at α=0.002. If the PFS null hypotheses in the ESCC

and the PDL1 CPS ≥10 populations are rejected and all the OS hypotheses are rejected, the PFS null hypothesis in all subjects may be tested at α=0.025.

Table 16 shows the boundary properties for PFS at the IA for each of these α levels, assuming the estimated numbers of events are analyzed. IA will be the final analysis for PFS.

Note that the final row indicates the total power to reject the null hypothesis for PFS at each α level. Also, note that if the OS null hypothesis in all subjects is rejected at the final analysis, PFS in all subjects may be tested again at the time of the final analysis using the interim data with its updated bounds, considering the α reallocation from the OS hypothesis.

Table 16 Efficacy Boundaries and Properties for Progression-free Survival Analyses

Analysis for ESCC	**Value**	**α=0.002**	
IA (Final):100%* N = 547 Events: 460 Month: 35	Z	2.878	
	p (1-sided) [a]	0.002	
	HR at bound[b]	0.765	
	P(Cross) if HR=1[c]	0.002	
	P(Cross) if HR=0.7[d]	0.828	
Analysis for PD-L1 CPS ≥10	**Value**	**α=0.002**	
IA (Final):100%* N = 381 Events: 320 Month: 35	Z	2.878	
	p (1-sided) [a]	0.002	
	HR at bound[b]	0.725	
	P(Cross) if HR=1[c]	0.002	
	P(Cross) if HR=0.7[d]	0.622	
Analysis for All Subjects	**Value**	**α=0.002**	**α=0.025**
IA (Final):100%* N = 749 Events: 630 Month: 35	Z	2.878	1.960
	p (1-sided) [a]	0.002	0.025
	HR at bound[b]	0.795	0.855
	P(Cross) if HR=1[c]	0.002	0.025
	P(Cross) if HR=0.75[d]	0.768	0.951

Abbreviations: HR = hazard ratio; IA = interim OS analysis; PD-L1 = programmed cell death-ligand 1.
The number of events and timings are estimated approximately.
*Percentage of the target number of events at final analysis anticipated at interim analysis
[a]*p* (1-sided) is the nominal α for testing.
[b]HR at bound is the approximate HR required to reach an efficacy bound.
[c]P (Cross if HR=1) is the probability of crossing a bound under the null hypothesis.
[d]P(Cross if HR=0.xx) is the probability of crossing a bound under the alternative hypothesis.

8.8.1.2 Overall Survival

The initial α assigned to the OS hypothesis in ESCC with PD-L1 CPS ≥10 will be 0.012; the initial α assigned to OS in ESCC will be 0.011; and the initial α assigned to OS in PD-L1 CPS ≥10 and OS in all subjects will be 0. If the OS hypothesis in ESCC with PD-L1 CPS ≥10 is rejected, half of the α will be reallocated to OS in ESCC and half will be reallocated to OS in PD-L1 CPS ≥10. If OS hypothesis in ESCC is rejected, that α will be reallocated to OS in PD-L1 CPS ≥10. Thus, the OS null hypothesis in ESCC may be tested at α=0.011 if the OS null hypothesis in ESCC with PD-L1 CPS ≥10 is not rejected, or at α=0.017 if the OS null hypothesis in ESCC with PD-L1 CPS ≥10 is rejected; the OS null hypothesis in PD-L1 CPS ≥10 may be tested at α=0.006 if the OS null hypothesis in ESCC with PD-L1 CPS ≥10 is rejected and the OS null hypothesis in ESCC is not rejected, or at α=0.011 if the OS null hypothesis in ESCC with PD-L1 CPS ≥10 is not rejected and the OS null hypothesis in ESCC is rejected, or at α=0.023 if the OS null hypotheses in ESCC with PD-L1 CPS ≥10 and in ESCC are both rejected. If OS hypothesis in PD-L1 CPS ≥10 is rejected, the α will be reallocated to OS hypothesis in all subjects. If all PFS null hypotheses are rejected, 0.99 of the α initially allocated to PFS hypotheses (α=0.002) will be reallocated to OS hypothesis in all subjects. Thus, the OS null hypothesis in all subjects may be tested at α=0.023 if the OS null hypotheses in all populations are rejected and any PFS null hypotheses are not rejected, or at α=0.025 if the OS null hypotheses in all populations and all PFS null hypotheses are rejected.

Table 17 shows the bounds and boundary properties for OS hypothesis testing derived using a Lan-DeMets O'Brien-Fleming spending function.

Table 17 Efficacy Boundaries and Properties for Overall Survival Analyses

Analysis in ESCC with PD-L1 CPS≥10	**Value**	**α=0.012**		
IA : 86%* N = 285 Events: 200 Month: 35	Z	2.473		
	p (1-sided)[a]	0.007		
	HR at bound[b]	0.705		
	P(Cross) if HR=1[c]	0.007		
	P(Cross) if HR=0.65[d]	0.721		
Final: 100%* N = 285 Events: 233 Month: 44	Z	2.324		
	p (1-sided)[a]	0.010		
	HR at bound[b]	0.737		
	P(Cross) if HR=1[c]	0.012		
	P(Cross) if HR=0.65[d]	0.845		
Analysis in ESCC	**Value**	**α=0.011**	**α=0.017**	
IA : 86%* N = 547 Events: 391 Month: 35	Z	2.507	2.325	
	p (1-sided)[a]	0.006	0.010	
	HR at bound[b]	0.776	0.790	
	P(Cross) if HR=1[c]	0.006	0.010	
	P(Cross) if HR=0.72[d]	0.773	0.824	
Final: 100%* N = 547 Events: 455 Month: 44	Z	2.356	2.194	
	p (1-sided)[a]	0.009	0.014	
	HR at bound[b]	0.802	0.814	
	P(Cross) if HR=1[c]	0.011	0.017	
	P(Cross) if HR=0.72[d]	0.883	0.913	

Analysis in PD-L1 CPS≥10	**Value**	**α=0.006**	**α=0.011**	**α=0.023**
IA : 86%* N = 381 Events: 267 Month: 35	Z	2.745	2.508	2.193
	p (1-sided)[a]	0.003	0.006	0.014
	HR at bound[b]	0.715	0.736	0.765
	P(Cross) if HR=1[c]	0.003	0.006	0.014
	P(Cross) if HR=0.65[d]	0.784	0.847	0.909
Final: 100%* N = 381 Events: 311 Month: 44	Z	2.568	2.356	2.075
	p (1-sided)[a]	0.005	0.009	0.019
	HR at bound[b]	0.747	0.766	0.790
	P(Cross) if HR=1[c]	0.006	0.011	0.023
	P(Cross) if HR=0.65[d]	0.899	0.932	0.962
Analysis in All Subjects	**Value**	**α=0.023**	**α=0.025**	
IA : 86%* N = 749 Events: 539 Month: 35	Z	2.192	2.154	
	p (1-sided)[a]	0.014	0.016	
	HR at bound[b]	0.828	0.831	
	P(Cross) if HR=1[c]	0.014	0.016	
	P(Cross) if HR=0.75[d]	0.875	0.883	
Final: 100%* N = 749 Events: 627 Month: 44	Z	2.075	2.042	
	p (1-sided)[a]	0.019	0.021	
	HR at bound[b]	0.847	0.850	
	P(Cross) if HR=1[c]	0.023	0.025	
	P(Cross) if HR=0.75[d]	0.942	0.946	

Abbreviations: HR = hazard ratio; IA = interim analysis.
The number of events is estimated approximately. The timing is estimated based on minimal follow-up requirement.
*Percentage of the target number of events at final analysis anticipated at interim analysis.
[a]*p* (1-sided) is the nominal α for testing.
[b]HR at bound is the approximate HR required to reach an efficacy bound.
[c]P(Cross if HR=1) is the probability of crossing a bound under the null hypothesis.
[d]P(Cross if HR=0.xx) is the probability of crossing a bound under the alternative hypothesis.

The bounds provided in the table above are based on the assumption that the expected number of events at IA and FA are 200 and 233 in ESCC with PD-L1 CPS ≥10, 391 and 455 in ESCC, 267 and 311 in PD-L1 CPS ≥10, 539 and 627 in all subjects, respectively. At the time of an analysis, the observed number of events may differ substantially from the expected. To avoid overspending at the interim analysis and leave reasonable alpha for the final analysis, the minimum alpha spending strategy will be adopted. At the IA, the information fraction used in Lan-DeMets spending function to determine the alpha spending at the IA will be based on the minimum of the expected information fraction and the actual information fraction at each analysis. Specifically,

- In the scenario that the events accrue faster than expected and the observed number of events exceeds the expected number of events at a given analysis, then the information fraction will be calculated as the expected number of events at the interim analysis over the target number of events at FA.

The final analysis will use the remaining Type I error that has not been spent at the earlier analyses. The boundary calculation will be based on the correlation between IA and FA test statistics, which is determined by the actual number of events observed at IA and FA.

8.8.1.3 Objective Response Rate

The study will test ORR only once at the interim analysis (IA), at an α level of 0.025 if all OS and PFS hypotheses are rejected. Note that if superiority for all PFS and OS hypotheses is declared at a future planned analysis, then the test statistics previously computed at IA for the ORR hypothesis will be used for inferential testing at an α level of 0.025.

Based on the 749 randomized subjects with at least 10 months of follow-up, power at α=0.025 as well as the approximate treatment difference required to reach the bound (ΔORR) are shown in Table 18, assuming underlying 35% and 50% response rates in the control and experimental groups, respectively.

Table 18 Possible α Levels and Approximate Objective Response Rate Difference Required to Demonstrate Efficacy for Objective Response at Interim Analysis

α	Approximate treatment difference in ORR	**Power (ΔORR=0.15)**
0.025	0.070	0.987

8.8.2 Multiplicity Control for Safety Analyses

To account for any multiplicity concerns raised by the DMC review of unplanned efficacy data when prompted by safety concerns, a sensitivity analysis for PFS by investigator and OS will be pre-specified in the sSAP. This analysis will be performed if requested by the DMC. However, DMC review of PFS by investigator and OS data beyond the planned efficacy analysis to assess the overall risk:benefit to trial subjects will not require multiplicity

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.

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.

8.12 Extent of Exposure

The extent of exposure will be summarized as duration of treatment in cycles.

9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.1 Investigational Product

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

Clinical Supplies will be provided by the Sponsor as summarized in Table 19

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

Table 19 Product Descriptions

Product Name & Potency	Dosage Form	Source/Additional Information
MK-3475 25 mg/mL (pembrolizumab)	Injection	Provided centrally by the Sponsor
5-Fluorouracil 50 mg/mL	Injection	Rest of World Provided centrally by the Sponsor or locally by the trial site, subsidiary, or designee
5-Fluorouracil 25 mg/mL	Injection	China only Provided centrally by the Sponsor or locally by the trial site, subsidiary, or designee
Cisplatin 1 mg/mL*	Injection	Rest of World Provided centrally by the Sponsor or locally by the trial site, subsidiary, or designee
Cisplatin 20 mg/vial	Injection	China only Provided centrally by the Sponsor or locally by the trial site, subsidiary, or designee

*Note: concentration may be different for products sourced in Japan

All supplies indicated in Table 19 will be provided per the "Source/Additional Information" column depending on local country operational requirements.

Any commercially available product not included in Table 19 will be provided by the trial site, subsidiary or designee. Every attempt should be made to source these supplies from a single lot/batch number. The trial site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product as per local guidelines unless otherwise instructed by the Sponsor.

9.2 Packaging and Labeling Information

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

Site pharmacies will receive open-label kits. Each MK-3475 kit will contain 2 vials. Each 5-FU kit and each cisplatin kit will contain 1 vial.

9.3 Clinical Supplies Disclosure

This trial is blinded but supplies are provided open label; therefore, an unblinded pharmacist or qualified trial site personnel will be used to blind supplies. Treatment identity (name, strength or potency) is included in the label text; random code/disclosure envelopes or lists are not provided.

The emergency unblinding call center will use the treatment/randomization schedule for the trial to unblind subjects and to unmask study treatment identity. The emergency unblinding call center should only be used in cases of emergency (see Section 7.1.4.2). In the event that the emergency unblinding call center is not available for a given site in this trial, the central electronic treatment allocation/randomization system (IVRS/IWRS) should be used in order to unblind subjects and to unmask treatment/vaccine identity. The Sponsor will not provide random code/disclosure envelopes or lists with the clinical supplies.

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.

9.4 Storage and Handling Requirements

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

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

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

9.5 Discard/Destruction/Returns and Reconciliation

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

9.6 Standard Policies

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

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

10.1 Confidentiality

10.1.1 Confidentiality of Data

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

10.1.2 Confidentiality of Subject Records

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

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

10.1.3 Confidentiality of Investigator Information

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

1. name, address, telephone number and e-mail address;
2. hospital or clinic address and telephone number;
3. curriculum vitae or other summary of qualifications and credentials; and
4. other professional documentation.

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

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

10.1.4 Confidentiality of IRB/IEC Information

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

10.2 Compliance with Financial Disclosure Requirements

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

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

10.3 Compliance with Law, Audit and Debarment

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

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

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

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

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

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

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

when documents may be destroyed. The Sponsor will determine the minimum retention period and upon request, will provide guidance to the investigator when documents no longer need to be retained. The Sponsor also recognizes that documents may need to be retained for a longer period if required by local regulatory requirements. All trial documents shall be made available if required by relevant regulatory authorities. The investigator must consult with and obtain written approval by the Sponsor prior to destroying trial and/or subject files.

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

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

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

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

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

10.4 Compliance with Trial Registration and Results Posting Requirements

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

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

10.5 Quality Management System

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

10.6 Data Management

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

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

10.7 Publications

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

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

and hypotheses, the subject inclusion and exclusion criteria, the trial design and procedures, the efficacy and safety measures, the statistical analysis plan, and any amendments relating to those sections. The Sponsor reserves the right to redact proprietary information.

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

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

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

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12.0 APPENDICES

12.1 Merck Code of Conduct for Clinical Trials

Merck*
Code of Conduct for Clinical Trials

I. Introduction

A. Purpose

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

B. Scope

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

II. Scientific Issues

A. Trial Conduct

1. Trial Design

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

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

2. Site Selection

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

3. Site Monitoring/Scientific Integrity

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

B. Publication and Authorship

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

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

III. Subject Protection

A. IRB/ERC review

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

B. Safety

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

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

C. Confidentiality

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

D. Genomic Research

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

IV. Financial Considerations

A. Payments to Investigators

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

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

B. Clinical Research Funding

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

C. Funding for Travel and Other Requests

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

V. Investigator Commitment

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

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

12.2 Collection and Management of Specimens for Future Biomedical Research

1. Definitions

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

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

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

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research

The specimens consented and/or collected in this trial as outlined in Section 7.1.3.6 – Future Biomedical Research Samples will be used in various experiments to understand:

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

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

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

3. Summary of Procedures for Future Biomedical Research

a. Subjects for Enrollment

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

b. Informed Consent

Informed consent for specimens (i.e., DNA, RNA, protein, etc.) will be obtained during screening for protocol enrollment from all subjects or legal guardians, at a trial visit by the investigator or his or her designate. Informed consent for Future Biomedical Research should be presented to the subjects on the visit designated in the trial flow chart. If delayed, present consent at next possible Subject Visit. Consent forms signed by the subject will be kept at the clinical trial site under secure storage for regulatory reasons.

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

c. eCRF Documentation for Future Biomedical Research Specimens

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

d. Future Biomedical Research Specimen(s)

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

4. Confidential Subject Information for Future Biomedical Research

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

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

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

5. Biorepository Specimen Usage

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

6. Withdrawal From Future Biomedical Research

Subjects may withdraw their consent for Future Biomedical Research and ask that their biospecimens not be used for Future Biomedical Research. Subjects may withdraw consent at any time by contacting the principal investigator for the main trial. If medical records for the main trial are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@merck.com).

Subsequently, the subject's specimens will be flagged in the biorepository and restricted to main study use only. If specimens were collected from study participants specifically for Future Biomedical Research, these specimens will be removed from the biorepository and destroyed. Documentation will be sent to the investigator confirming withdrawal and/or destruction, if applicable. It is the responsibility of the investigator to inform the subject of completion of the withdrawal and/or destruction, if applicable. Any analyses in progress at the time of request for withdrawal/destruction or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research trial data and results. No new analyses would be generated after the request is received.

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

7. Retention of Specimens

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

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

8. Data Security

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

9. Reporting of Future Biomedical Research Data to Subjects

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

If important research findings are discovered, the Sponsor may publish results, present results in national meetings, and make results accessible on a public website in order to rapidly report this information to doctors and subjects. Subjects will not be identified by

name in any published reports about this study or in any other scientific publication or presentation.

10. Future Biomedical Research Study Population

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

11. Risks Versus Benefits of Future Biomedical Research

For FBR, risks to the subject have been minimized. No additional risks to the subject have been identified as no additional specimens are being collected for FBR (i.e., only leftover samples are being retained).

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

12. Questions

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

13. References

1. National Cancer Institute: http://www.cancer.gov/dictionary/?searchTxt=biomarker
2. International Conference on Harmonization: DEFINITIONS FOR GENOMIC BIOMARKERS, PHARMACOGENOMICS, PHARMACOGENETICS, GENOMIC DATA AND SAMPLE CODING CATEGORIES - E15; http://www.ich.org/LOB/media/MEDIA3383.pdf
3. Industry Pharmacogenomics Working Group. Understanding the Intent, Scope and Public Health Benefits of Exploratory Biomarker Research: A Guide for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/
4. Industry Pharmacogenomics Working Group. Pharmacogenomics Informational Brochure for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/

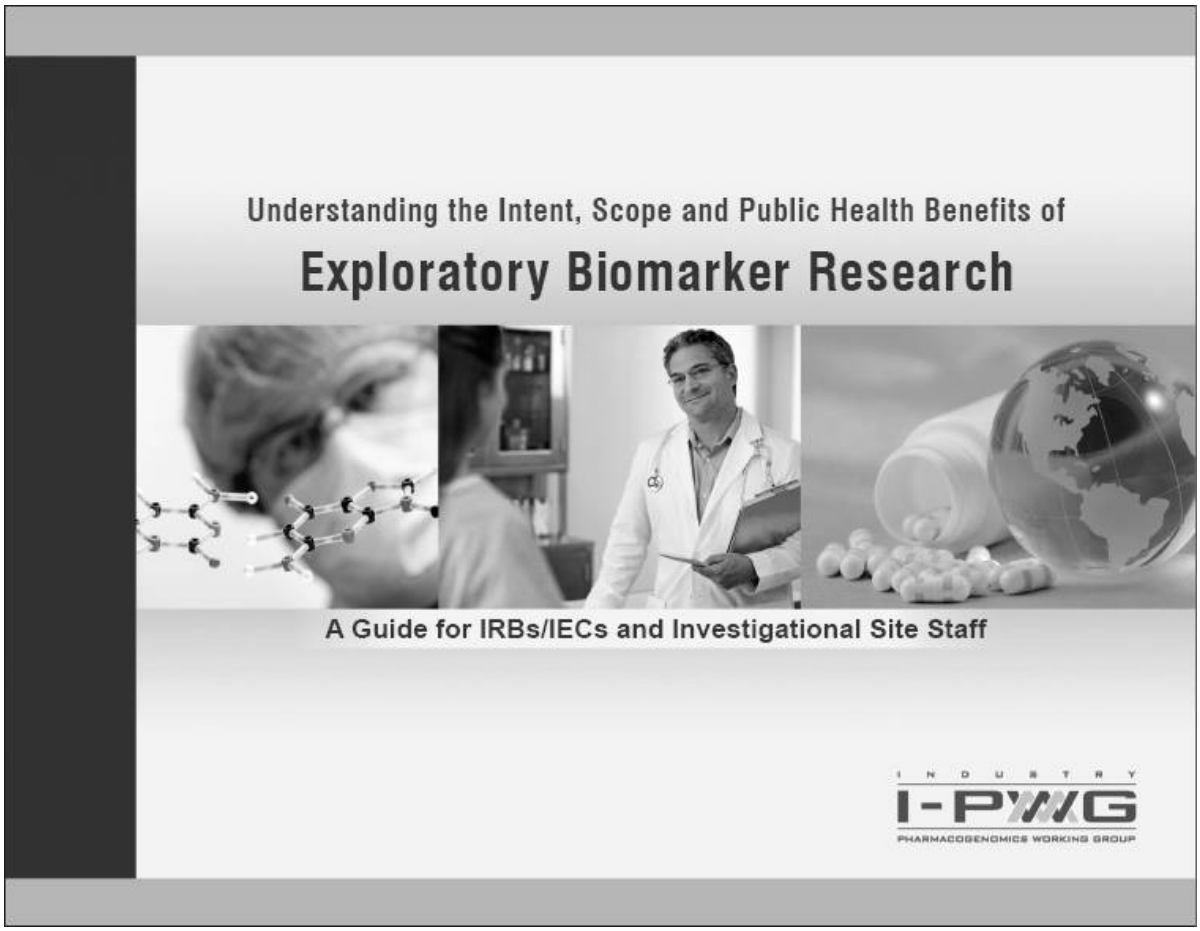
Note that Future Biomedical Research is not applicable for China.

12.3 ECOG Performance Status

Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of light or sedentary nature, e.g., light housework, office work.
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.
5	Dead.

* As published in Am. J. Clin. Oncol.: *Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.* The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair. [41]

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



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

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

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

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

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

2. Why is Biomarker Research Important?

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

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

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

1

I-PWG

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

3. Importance of Biomarkers to Regulatory Authorities

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

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

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

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

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

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5. Biomarkers are Already a Reality in Health Care

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

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

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

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

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

6. Biomarker Samples from Clinical Trials: An Invaluable Resource

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

7. Informed Consent for Collection & Banking of Biomarker Samples

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

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and regulations for legally-appropriate informed consent vary on national, state, and local levels, but are generally based on internationally recognized pillars of ethical conduct for research on human subjects.[28-31]

Optional vs. Required Subject Participation

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

Consent for Future Research Use

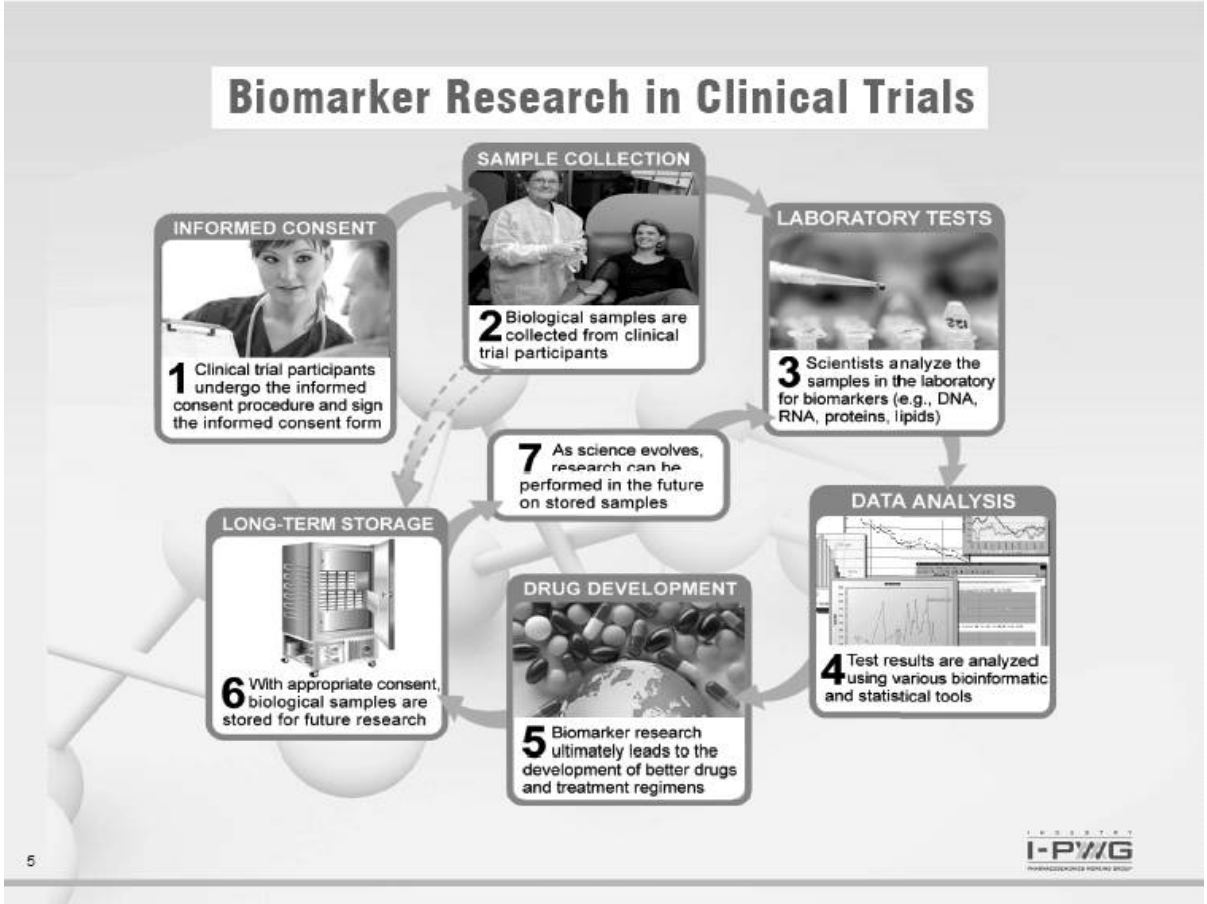
While it can be a challenge to specify the details of the research that will be conducted in the future, the I-PWG holds the view that future use of samples collected for exploratory biomarker research in clinical trials should be permissible when i) the research is scientifically sound, ii) participants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

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

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

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

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


Biomarker Research in Clinical Trials
SAMPLE COLLECTION
2 Biological samples are collected from clinical trial participants
INFORMED CONSENT
1 Clinical trial participants undergo the informed consent procedure and sign the informed consent form
LABORATORY TESTS
3 Scientists analyze the samples in the laboratory for biomarkers (e.g., DNA, RNA, proteins, lipids)
7 As science evolves, research can be performed in the future on stored samples
DATA ANALYSIS
4 Test results are analyzed using various bioinformatic and statistical tools
LONG-TERM STORAGE
6 With appropriate consent, biological samples are stored for future research
DRUG DEVELOPMENT
5 Biomarker research ultimately leads to the development of better drugs and treatment regimens
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8. Biomarker Sample Collection in Different Countries

Collection of biological samples for biomarker research is straightforward in most jurisdictions. Some countries have specific laws and regulations regarding collection, labeling, storage, export, and/or use of exploratory samples. In addition, some regulations distinguish between DNA and non-DNA samples or between samples used for diagnostic purposes and samples collected for scientific research. Processes for the collection, labeling, storage, export, and/or use of biomarker samples should always adhere to the laws and regulations of the country/region in which those samples are collected.

9. Return of Research Results to Study Participants

Policies for the return of biomarker research results to study participants who request them vary among pharmaceutical companies. There are many considerations that pharmaceutical companies weigh when determining their policy regarding the return of biomarker research results to study participants. These include:

i) the conditions under which biomarker research results were generated (i.e., exploratory research laboratory versus accredited diagnostic laboratory)

ii) whether the results will have an impact on the medical care of the participant or on a related person, if applicable

iii) whether genetic counseling is recommended (for genetic results)

iv) the ability to accurately link the result to the individual from whom the sample was collected

v) international, national, and local guidelines, policies, legislation, and regulations regarding participants' rights to access data generated on them

Renegar *et al*. 2006 and Article 29 Data Protection Working Party (an advisory committee to the European Commission on the European Data Protection Directive) have addressed these considerations in detail in relation to pharmacogenomic research data and provided a list of documents addressing the general issue of return of research results.[34-35]

10. Benefits and Risks Associated with Biomarker Research

Benefits

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

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

Risks

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

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

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

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

11. Privacy, Confidentiality, and Patient Rights

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

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

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

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

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

12.Where to Get More Information?

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

13. What is I-PWG?

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

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

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Note that Future Biomedical Research is not applicable for China.

12.5 List of Abbreviations

Abbreviation/Term	Definition
5-FU	5-fluorouracil
ADA	anti-drug antibody
ADL	activities of daily living
AE	adverse event
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
ASaT	all subjects as treated
AST	aspartate aminotransferase
BICR	blinded independent central review
BP	blood pressure
BUN	blood urea nitrogen
CBC	complete blood count
CI	confidence interval
CPS	Combined positive score
CR	complete response
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	cytotoxic T-lymphocyte-associated protein-4
DL	dose level
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DOR	duration of response
ECG	electrocardiogram
ECI	event of clinical interest
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
ePRO	electronic patient-reported outcome
EGJ	esophagogastric junction
EMA	European Medicines Agency
EOC	Executive Oversight Committee
EORTC	European Organization for the Research and Treatment of Cancer

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

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

Abbreviation/Term	Definition
RNA	ribonucleic acid
RR	respiratory rate
SAC	Scientific Advisory Committee
SAE	serious adverse event
SAP	statistical analysis plan
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SOC	system organ class
SOP	Standard Operating Procedures
sSAP	supplemental statistical analysis plan
T	temperature
T3	triiodothyronine
T1DM	type 1 diabetes mellitus
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
WBC	white blood cell
WES	Whole exome sequencing

12.6 Country-specific Appendix

12.6.1 France-specific Requirements

- Exclusion Criterion #10: Note: Sites in France will perform a systematic search for dihydropyrimidine dehydrogenase deficiency for subjects who are naive to 5-FU. This research should be performed before any administration of 5-FU.
- Additional Exclusion Criterion # 21: Has active, clinically significant cardiac disease or a history of myocardial infarction in the last 6 months or cardiorespiratory pathology which precludes hyperhydration for cisplatin therapy.
- Additional Exclusion Criterion # 22: Subjects with Grade ≥2 audiometric hearing loss (25 decibels in 2 consecutive wave ranges) are not eligible for treatment with cisplatin.
- Section 5.6.1: Pembrolizumab is to be permanently discontinued in cases of confirmed Stephens-Johnson Syndrome, toxic epidermal necrolysis/Lyell syndrome, recurrent Grade 3 colitis, and Grade 4 skin rash.
- Section 5.6.2 and Section 5.6.3: For subjects receiving cisplatin and 5-FU: Please refer to the updated SmPC for these marketed products or the website http://base-donnees-publique.medicaments.gouv.fr/, which presents the updated version of the SmPC of the medicines.
- Section 7.1.2.2.1 and Section 7.1.2.2.2: Audiometry testing must be performed before each cisplatin treatment cycle.

13.0 SIGNATURES

13.1 Sponsor's Representative

TYPED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	

13.2 Investigator

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

TYPED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	