Official Protocol Title:	A Randomized, Active-Controlled, Partially Blinded, Biomarker Select, Phase III Clinical Trial of Pembrolizumab as Monotherapy and in Combination with Cisplatin+5-Fluorouracil versus Placebo+Cisplatin+5-Fluorouracil as First-Line Treatment in Subjects with Advanced Gastric or Gastroesophageal Junction (GEJ) Adenocarcinoma
NCT number:	NCT02494583
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TITLE:

A Randomized, Active-Controlled, Partially Blinded, Biomarker Select, Phase III Clinical Trial of Pembrolizumab as Monotherapy and in Combination with Cisplatin+5-Fluorouracil versus Placebo+Cisplatin+5-Fluorouracil as First-Line Treatment in Subjects with Advanced Gastric or Gastroesophageal Junction (GEJ) Adenocarcinoma

IND NUMBER: 123,482

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DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
3475-062-13	23-Jan-2019	Clarification of language in various protocol sections related to AEs, follow-up, and supportive care
3475-062-12	08-Jan-2019	Clarification of language in various protocol sections related to AEs, follow-up, and supportive care
3475-062-11	27-Apr-2018	Added 2 more primary OS hypotheses; clarified AE language
3475-062-10	05-Apr-2018	Added 2 more primary OS hypotheses; clarified AE language
3475-062-09	08-Jan-2018	Revised dose modification table and survival status data collection requirements; updated SAP
3475-062-08	01-Dec-2017	Revised dose modification table and survival status data collection requirements; updated SAP
3475-062-07	24-Mar-2017	Revised primary and secondary objectives
3475-062-06	07-Mar-2017	Revised primary and secondary objectives
3475-062-05	08-Sep-2016	Update information related to pregnancy and contraception

Document	Date of Issue	Overall Rationale
3475-062-04	08-Sep-2016	Clarify that subjects with locally advanced adenocarcinoma only include those whose tumors are unresectable.
3475-062-03	15-Jul-2016	Clarify that subjects with locally advanced adenocarcinoma only include those whose tumors are unresectable
3475-062-02	29-Sep-2015	Addition of monitoring for SOC side effects and prohibited concomitant medications that are contraindicated with SOC therapies.
3475-062-01	25-Sep-2015	Capecitabine must be provided centrally by the Sponsor for Japan.
3475-062-00	05-May-2015	Original Protocol

SUMMARY OF CHANGES

PRIMARY REASON(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
4.2.3.3	Rationale for Safety Endpoints	Last sentence deleted	To remove outdated reference to Section 7.2.3.2 since the content in that section has been changed
5.5.2	Prohibited Concomitant Medication	Language adjustment in "Prohibited systemic glucocorticoids for any purpose other than to modulate symptoms from an **AE** of suspected immunologic etiology or cisplatin supportive care."	Editorial change
5.6.1	Supportive Care Guidelines	Section heading changed into "Supportive Care Guidelines for Pembrolizumab"; ; deleted note related to ECIs	To add clarification
5.6.1	Supportive Care Guidelines	Updated reference to supportive care procedures for the management of AE with potential immunologic etiology	To update reference

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
6.1.1	Treatment Arm 1: Pembrolizumab Monotherapy	Safety Follow-up changed from "30 days post last dose into "30 days post discontinuation"	To add clarification
6.1.2	Treatment Arm 2 and 3: Pembrolizumab + Chemotherapy and Placebo + Chemotherapy	Follow-up Visit changed from "Every 6 weeks post last dose" into "Every 6 weeks post discontinuation"	To add clarification
6.2	Second Course Phase (Retreatment with Pembrolizumab)	Safety Follow-up changed from "30 days post last dose" into "30 days post discontinuation"	To add clarification
7.1.2.1	Adverse Event (AE) Monitoring	Deleted the paragraph about ECI identification and management with reference to the ECI guidance document	To remove redundant and obsolete information as the ECI Guidance Document was retired in 2015.
7.2.3.2	Events of Clinical Interest	Deleted Item #3 Additional adverse events	To remove redundant and obsolete information as the ECI Guidance Document was retired in 2015.

ADDITIONAL CHANGE(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
Throughout the protocol	Correct typographical errors	Correct typographical errors for better clarity	Throughout the protocol

No additional changes.

1.0 TRIAL SUMMARY

Abbreviated Title	Phase III Trial of Pembrolizumab (MK-3475), pembrolizumab+FP/XP vs. Placebo+FP/XP in Biomarker Select, Advanced Gastric or GEJ Adenocarcinoma
Trial Phase	III
Clinical Indication	Advanced Gastric or Gastroesophageal Junction (GEJ) Adenocarcinoma
Trial Type	Interventional
Type of control	Active control
Route of administration	Intravenous
Trial Blinding	Partially Blinded: **Treatment Arm 1**: Pembrolizumab (monotherapy); the subject, the trial site personnel, the Sponsor and/or designee will not be blinded to this treatment arm since only one type of study medication will be administered on this arm. **Treatment Arms 2 and 3:** pembrolizumab/placebo is blinded in the combination chemotherapy arms (pembrolizumab+chemotherapy and placebo+chemotherapy, respectively) of this trial to the subject, site personnel and SPONSOR. Pembrolizumab monotherapy (Arm 1) and pembrolizumab/placebo in the combination chemotherapy arms (Arms 2 & 3) will be prepared in a blinded fashion by an assigned unblinded pharmacist or qualified trial site personnel. The investigator or qualified site personnel will administer pembrolizumab/placebo to subjects in Treatment Arms 2 and 3 in a blinded fashion, therefore subjects, site personnel and sponsor personnel are blinded to pembrolizumab/placebo treatment for these 2 arms.
Treatment Groups	Treatment Arm 1: Pembrolizumab monotherapy 200 mg fixed dose administered every 3 weeks (Q3W) Treatment Arm 2: Pembrolizumab 200 mg fixed dose Q3W + Cisplatin 80 mg/m^2 Q3W + 5-FU* 800 mg/m^2/day continuous IV infusion Days 1-5 (120 hours) Treatment Arm 3: Placebo Q3W + Cisplatin 80 mg/m^2 Q3W + 5-FU* 800 mg/m^2/day continuous IV infusion Days 1-5 (120 hours) *Although use of 5-FU infusion is preferred, capecitabine 1000 mg/m2 twice a day (BID) D1-14 Q3W may be permitted according to local guidelines. Investigator decision regarding the type of comparator used (5-FU or capecitabine) should be determined prior to randomization. Subjects should continue on the therapy chosen prior to randomization throughout the study. Exceptions may be permitted after consultation with the Sponsor.
Number of trial subjects	Approximately 750 subjects will be enrolled.
Estimated duration of trial	The sponsor estimates that the trial will require approximately 44 months from the time the first subject signs the informed consent until the last subject's last visit.
Duration of Participation	Each subject will participate in the trial from the time the subject signs the Informed Consent Form (ICF) through the final protocol-specified contact.

	After a screening phase 28 days, each subject will be assigned to receive trial treatment until disease progression is radiographically documented and verified by blinded independent central review (BICR), when clinically appropriate, confirmed by the site per immune related Response Evaluation Criteria in Solid Tumors (irRECIST) for subjects treated with pembrolizumab, unacceptable adverse event(s) (AEs), intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw 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 (approximately 2 years). **Subjects** who stop trial treatment after **receiving** 35 administrations of pembrolizumab for reasons other than **disease** progression or intolerability, or subjects who attain a complete response (CR) and stop trial treatment may be eligible for up to 17 additional administrations of pembrolizumab (approximately 1 year) upon experiencing disease progression (Section 7.1.5.3). After the end of treatment, each subject will be followed for the occurrence of AEs and spontaneously reported pregnancy as described under Section 7.2. Subjects who discontinue for reasons other than radiographic disease progression will have post-treatment follow-up imaging for disease status until disease progression, is documented radiographically per RECIST 1.1, confirmed by the site per irRECIST (for subjects treated with pembrolizumab), initiating a non-trial 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	1:1:1

A list of abbreviations used in this document can be found in Section 12.8.

2.0 TRIAL DESIGN

2.1 Trial Design

This is a randomized, active-controlled, multi-site, partially blinded, trial of pembrolizumab, or pembrolizumab+cisplatin+5-fluorouracil (5-FU) versus placebo+cisplatin+5-FU, as first-line treatment in programmed death-ligand 1 (PD-L1) positive (ie Combined Positive Score (CPS)≥1), human epidermal growth factor receptor 2 (HER2/neu) negative subjects with advanced gastric or gastroesophageal junction (GEJ) adenocarcinoma.

Approximately 750 subjects will be randomized to compare the efficacy and safety of pembrolizumab or pembrolizumab+cisplatin +5-FU versus placebo+cisplatin+5-FU as first-line treatment. Although use of 5-FU infusion is preferred, capecitabine may be used according to local guidelines at the investigator's discretion. Investigator decision regarding the type of comparator used (5-FU or capecitabine) must be determined prior to

randomization in the trial. Subjects should continue on the backbone therapy chosen prior to randomization throughout the study. Exceptions may be permitted after consultation with the Sponsor.

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

Subjects will be randomized in a 1:1:1 ratio among the three treatment arms as listed below (Table 1), stratified by geographic region, disease status, and backbone therapy treatment (see Section 5.4 Stratification for more details).

Table 1 Treatments Dose and Schedule

Treatment Arm	Treatment Dose and Schedule
Treatment Arm 1	Pembrolizumab 200 mg every 3 weeks (Q3W)
Treatment Arm 2*	Pembrolizumab 200 mg Q3W+ Cisplatin 80 mg/m^2 Q3W+5-FU 800 mg/m^2/day continuous IV infusion Days 1-5 (120 hours)
Treatment Arm 3*	Placebo Q3W +Cisplatin 80 mg/m^2 Q3W+5-FU 800 mg/m^2/day continuous IV infusion Days 1-5 (120 hours)

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

*Although use of 5-FU infusion is preferred, capecitabine1000 mg/m2 bid D1-14 Q3W can be used according to the local guideline. Investigator decision regarding the type of comparator used (5-FU or capecitabine) should be determined prior to randomization in the trial. Subjects should continue on the backbone therapy chosen prior to randomization throughout the study. Exceptions may be permitted after consultation with the Sponsor. Duration of cisplatin treatment may be capped at 6 cycles as per local country guidelines, however treatment with 5-FU/capecitabine may continue per protocol.

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

This study is partially blinded:

Treatment Arm 1 (pembrolizumab monotherapy); the subject, the trial site personnel, the Sponsor and/or designee will not be blinded to this treatment arm since only one type of study medication will be administered on this arm.

Treatment Arms 2 and 3 pembrolizumab/placebo is blinded in the combination chemotherapy arms of this trial to the subject, site personnel and SPONSOR personnel.

Pembrolizumab monotherapy (Arm 1) and pembrolizumab/placebo in the combination chemotherapy arms (Arms 2 & 3) will be prepared in a blinded fashion by an assigned unblinded pharmacist or qualified trial site personnel. The investigator or qualified site personnel will administer pembrolizumab/placebo to subjects in Treatment Arms 2 and 3 in a blinded fashion, therefore subject, site personnel and sponsor personnel are blinded to pembrolizumab/placebo treatment for these 2 arms.

Participation in this trial will be dependent upon supplying a tumour tissue specimen. **Newly obtained endoscopic biopsy or core biopsy of a metastatic site if obtained as part of normal clinical practice is preferred to archive samples.** Both formalin solution and formalin-fixed, paraffin embedded (FFPE) block specimens are acceptable. If submitting unstained slides, the slides should be freshly cut and received at the testing laboratory within 14 days from site slide section date, otherwise a new specimen will be requested. The specimen will be evaluated at a central laboratory facility for expression status of PD-L1 in a prospective manner. Only subjects whose tumours express PD-L1 (are PD-L1+) as determined by the central laboratory facility will be eligible for randomization in this study. Subjects will also be required to be HER-2/neu negative.

Subjects will undergo the first imaging evaluation at week 6 (± 7 days) after subject has been randomized. Subsequently, subjects will be evaluated every 6 weeks (42 days ± 7 days), independent of any treatment delays, with radiographic imaging to assess response to treatment using Response Evaluation Criteria in Solid Tumors version 1.1. (RECIST.1.1). Study treatment will continue until first evidence of Progressive Disease (PD). RECIST 1.1 responses as assessed by the central vendor will be used as the primary efficacy endpoint; ie, Progression Free Survival (PFS). RECIST 1.1 will be used by the local site for treatment decisions until verification of PD by the central imaging vendor. Following verification of PD by central vendor, treatment decision may be made by the adaptation of RECIST 1.1 [1], as described in Section 7.1.2.7.1.1., termed immune-related RECIST (irRECIST) to accommodate for the tumour response patterns seen with pembrolizumab treatment (eg, tumour flare).

Adverse events (AE) will be monitored throughout the trial and graded in severity according to the guidelines outlined in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

Treatment will continue until documented clinical PD, unacceptable AE(s), 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, or administrative reasons.

Subjects receiving monotherapy or combination therapy that have evidence of PD by imaging and are clinically stable may continue to be treated at the discretion of the investigator. In addition, subjects who attain an investigator-determined confirmed complete response (CR) may consider stopping trial treatment after receiving at least 8 trial administrations in total and at least two additional administrations of study drug after achieving confirmed CR prior to treatment discontinuation.

Furthermore, subjects who stop pembrolizumab with stable disease (SD) or better may be eligible for up to 17 additional pembrolizumab therapies if they have experienced radiographic disease progression while off study treatment according to the criteria in Section 7.1.5.2.1. This retreatment is termed the Second Course Phase of this study and is only

available if the study remains open. Response or progression in the Second Course Phase will not count towards the PFS of the primary endpoint in this trial. The decision to retreat will be at the discretion of the investigator only if no cancer treatment was administered since the last dose of study treatment and the subject still meets the safety parameters listed in the Inclusion/Exclusion criteria (refer to Section 7.1.5.2.1 for further details).

For the abovementioned reasons, if treatment identification information for the combination treatment arms (pembrolizumab+chemotherapy and placebo+chemotherapy) is required then unblinding is allowed as per criteria in Section 7.1.4.2.

After the end of treatment, each subject will have a 30-day follow-up assessment for AE monitoring (serious adverse events [SAEs] and events of clinical interest [ECIs] will be collected for 90 days after the end of treatment or 30 days after the end of treatment if the subject initiates new anticancer therapy, 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 every 12 weeks (±7 days), or more often as needed, for overall survival (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 Practices.

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.

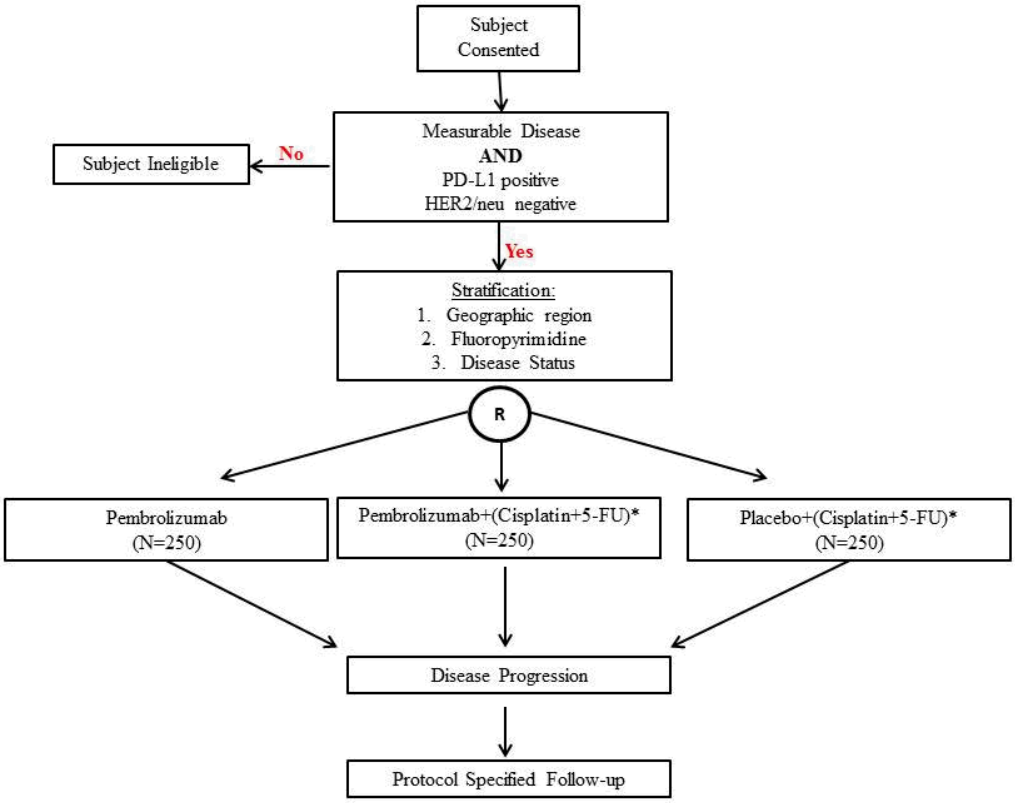
This trial will use a group sequential design based on pre-specified criteria, using an independent, external Data Monitoring Committee (eDMC) to monitor safety and efficacy.

There will be two interim efficacy analyses, one planned interim safety analysis, and periodic safety monitoring. The interim efficacy analyses are event-driven. The interim safety analysis will be conducted when at least 10 subjects in each treatment arm (at least 30 subjects total) have completed 1 cycle of treatment. Results of the interim analyses will be reviewed by an eDMC. More details are in Section 8.7.

There will be no pause in enrolment during the planned interim analyses.

2.2 Trial Diagram

The trial design is depicted in Figure 1 below.



*Although use of 5-FU infusion is preferred, capecitabine 1000 mg/m^2 bid Day1-14 Q3W may be permitted according to local guideline. Investigator decision regarding the type of comparator used (5-FU or capecitabine) should be determined prior to randomization in the trial. Subjects should continue on the fluoropyrimidine chosen prior to randomization throughout the study. Exceptions may be permitted after consultation with the Sponsor.

HER2/neu negative is defined as: IHC (0, or 1+), or FISH negative (HER2:CEP17 ratio < 2). FISH can be replaced with locally available ISH methods acceptable as per institutional guidelines (eg DISH).

Note that depending on emerging internal/external data, one or more of the arms may not be pursued.

Figure 1 Phase III Trial Design for Enrolment of PD-L1 Positive, HER2/neu Negative Subjects with Advanced Gastric or Gastroesophageal Junction (GEJ) Adenocarcinoma.

3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

3.1 Primary Objective(s) & Hypothesis(es)

(1) In subjects with advanced gastric or GEJ adenocarcinoma treated with pembrolizumab monotherapy or a combination of pembrolizumab with chemotherapy versus chemotherapy alone, as first-line treatment in subjects with PD-L1 positive expression **Objective 1:** Evaluate Progression Free Survival (PFS) per RECIST 1.1 as assessed by blinded central radiologists' review in subjects with PD-L1 Combined Positive Score (CPS) ≥1.

Hypothesis (H1): Pembrolizumab in combination with chemotherapy is superior to chemotherapy alone in terms of PFS per RECIST 1.1 by blinded central radiologists' review in subjects with PD-L1 CPS≥1.

(2) **Objective 2:** Evaluate overall survival (OS).

Hypothesis (H2): Pembrolizumab in combination with chemotherapy is superior to chemotherapy alone in terms of OS in subjects with PD-L1 CPS≥1.

Hypothesis (H3): Pembrolizumab in combination with chemotherapy is superior to chemotherapy alone in terms of OS in subjects with PD-L1 CPS ≥10.

Hypothesis (H4): Pembrolizumab monotherapy is non-inferior to chemotherapy alone in terms of OS in subjects with PD-L1 CPS≥1.

The statistical criterion for the success of Hypothesis H4 is that, if the upper bound of the confidence interval, based on the alpha level allocated to the analysis, for the hazard ratio (HR: monotherapy arm vs control) is < 1.2, the pembrolizumab monotherapy arm could be considered as non-inferior to the control arm in terms of OS.

Hypothesis (H5): Pembrolizumab monotherapy is superior to chemotherapy alone in terms of OS in subjects with PD-L1 CPS≥1.

Hypothesis (H6): Pembrolizumab monotherapy is superior to chemotherapy alone in terms of OS in subjects with PD-L1, CPS ≥10.

PD-L1 positive expression defined by CPS≥1 and by CPS ≥10 CPS; is henceforth abbreviated as PD-L1 CPS1 and PD-L1 CPS10, respectively.

The study is considered to have met its primary objective if at least one hypothesis, H1-H6 is significant at the interim or final analysis as defined in Section 8.8 Multiplicity.

3.2 Secondary Objective(s) & Hypothesis(es)

(1) **Objective**: Evaluate Overall Response Rate (ORR), and Duration of Response (DOR), per RECIST 1.1 as assessed by central radiologists in subjects with PD-L1 CPS≥1.

(2) .**Hypothesis (H7):** Pembrolizumab in combination with chemotherapy is superior to chemotherapy alone in terms of ORR per RECIST 1.1 as assessed by blinded central radiologists in subjects with PD-L1 CPS≥1.

(3) **Objective**: Evaluate Progression Free Survival (PFS) per RECIST 1.1 as assessed by blinded central radiologists' review in subjects treated with pembrolizumab.

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

(5) **Objective:** Evaluate changes in health-related quality-of-life assessments from baseline using the EORTC QLQ-C30 and the EORTC QLQ-STO22.

3.3 Exploratory Objectives

(1) **Objective**: Characterize utilities using the EuroQoL EQ5D-3L.

4.0 BACKGROUND & RATIONALE

4.1 Background

Pembrolizumab is a potent humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) with high specificity of binding to the programmed cell death 1 (PD-1) receptor, thus inhibiting its interaction with programmed cell death ligand 1 (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 brochure.

4.1.1 Pharmaceutical and Therapeutic Background

4.1.1.1 Pembrolizumab

Keytruda® (pembrolizumab) has recently been approved in the United States for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor.

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades [2]. Accumulating evidence shows a correlation between tumour-infiltrating lymphocytes (TILs) in cancer tissue and favourable prognosis in various malignancies [3; 4; 5; 6; 7]. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells / FoxP3+ regulatory T-cells seems to correlate with improved prognosis and long-term survival in many solid tumours.

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumours to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an Ig superfamily member related to CD28 and CTLA-4 which has been shown to negatively regulate antigen receptor signalling upon engagement of its ligands (PD-L1 and/or PD L2) [8;9]. The structure of murine PD-1 has been resolved [10]. PD-1 and family members are type I transmembrane glycoproteins containing an Ig Variable-type (V-type) domain responsible for ligand binding and a cytoplasmic tail which is responsible for the binding of signalling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signalling motifs, an immunoreceptor tyrosine-based inhibition motif (ITIM) and an immunoreceptor

tyrosine-based switch motif (ITSM). Following T-cell stimulation, PD 1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3ζ, PKCθ and ZAP70 which are involved in the CD3 T-cell signalling cascade [8; 11; 12; 13]. The mechanism by which PD-1 down modulates T-cell responses is similar to, but distinct from that of CTLA-4 as both molecules regulate an overlapping set of signalling proteins [14; 15]. PD-1 was shown to be expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B-cells, T regs and Natural Killer cells [16; 17]. Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells [18]. The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types, including non-hematopoietic tissues as well as in various tumours [19; 20; 21; 14]. Both ligands are type I transmembrane receptors containing both IgV- and IgC-like domains in the extracellular region and contain short cytoplasmic regions with no known signalling motifs. Binding of either PD-1 ligand to PD-1 inhibits T-cell activation triggered through the T-cell receptor. PD-L1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments. PD-L2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T-cell function in peripheral tissues [14]. Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. PD-1 has been suggested to regulate tumour-specific T-cell expansion in subjects with melanoma (MEL) [22].

In gastric cancer PD-L1 and PD-L2 overexpression have recently been associated with EBV-positive tumours [23]. This suggests that the PD-1/PD-L1 pathway plays a critical role in tumour immune evasion and can be an attractive target for therapeutic intervention.

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 tumour-specific CD8+ T-cells and leads ultimately to tumour rejection, either as a mono-therapy or in combination with other treatment modalities. Anti-mouse PD-1 or anti-mouse PD-L1 antibodies have demonstrated anti-tumour responses as a mono-therapy in models of squamous cell carcinoma, pancreatic carcinoma, MEL and colorectal carcinoma. Blockade of the PD-1 pathway effectively promoted CD8+ T-cell infiltration into the tumour and the presence of IFN-γ, granzyme B and perforin, indicating that the mechanism of action involved local infiltration and activation of effector T-cell function in vivo [24; 25; 26; 27; 28; 29]. Experiments have confirmed the in vivo efficacy of PD-1 blockade as a mono-therapy as well as in combination with chemotherapy in syngeneic mouse tumour models (see the Investigator's Brochure [IB]).

Clinical trials have demonstrated efficacy in subjects with advanced melanoma, non-small cell lung cancer, 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 are being conducted in advanced melanoma, non-small cell lung cancer, a number of advanced solid tumour indications and hematologic malignancies. For study details please refer to the IB.

4.1.3.1 Ongoing Clinical Trials in Gastric Cancer

Preliminary interim data is available from a cohort of gastric adenocarcinoma subjects studied in trial [KEYNOTE (KN012)] [30]. KEYNOTE-012 trial is a multi-cohort Phase IB study of which one cohort enrolled subjects with recurrent or metastatic gastric or GEJ adenocarcinoma that expressed PD-L1 (≥1% by immunohistochemistry). This cohort enrolled 39 subjects (19 from Asia and 20 outside Asia). The primary endpoint was overall response rate (ORR). Although 67% of subjects had received 2 or more prior chemotherapy lines, pembrolizumab monotherapy demonstrated an interim ORR of 33.3% by RECIST v.1.1 per investigator review (95% confidence interval [CI]: 19.1%, 50.2%; all partial responses). The interim disease control rate (DCR) was 41% (95% CI: 25.6%, 57.9%]). ORR was similar in subjects from Asia and outside of Asia, while the DCR was numerically higher in Asia. Responses were observed across all lines of treatment. Fifty-three percent of the subjects with measurable disease displayed some degree of tumour shrinkage from baseline. As of the data cut-off of 14 Nov 2014, the median duration of response was 24 weeks (6 months). Based on preliminary data there appears to be a correlation between response and degree of PD-L1 positivity.

In these gastric cancer subjects in KN012, single agent pembrolizumab at 10 mg/kg q2weeks was generally well tolerated, with the type, severity, and frequency of AEs similar to that observed in other indications (see the IB for information about AEs in other indications). There was 1 death reported in the gastric cancer cohort. This was a subject who had AEs of tracheomalacia (Grade 3) and hypoxia (Grade 5). The investigator considered the Grade 5 hypoxia related to study treatment.

4.1.4 Information on Other Trial-Related Therapy

A variety of chemotherapies are used for subjects with advanced, first line gastric and GEJ adenocarcinoma. Early studies demonstrated small survival benefits after treatment with cisplatin or chemotherapy combinations.

A number of ongoing Phase 3 trials are evaluating the addition of targeted monoclonal antibodies or small molecules to standard chemotherapy regimens. First positive result was shown from ToGA study comparing cisplatin/fluoropyrimidine plus trastuzumab, a monoclonal antibody against the human epidermal growth factor receptor 2 (HER2), with the same chemotherapy alone in subjects with HER2-positive gastric or gastroesophageal adenocarcinoma. The study demonstrated significantly improved OS associated with the trastuzumab-containing regimen over chemotherapy alone (median 13.5 and 11.1 months, respectively, p=.0048). The outcome of ToGA study supported the approval of Trastuzumab for HER2-positive gastric cancer subjects [31].

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

Trials evaluating pembrolizumab (MK-3475) in gastric cancer have demonstrated clinical activity in subjects with recurrent and/or metastatic disease. Refer to Section 4.1.3, Ongoing Clinical Trials, for results from the Phase Ib study of pembrolizumab in subjects with gastric cancer (KN012).

The gastric cancer proof-of-concept from KN012 data was obtained in subjects with a PD-L1 positive expression only; no data is currently available regarding the performance of pembrolizumab in subjects without a detectable PD-L1 expression.

4.2.2 Rationale for Dose Selection/Regimen/Modification

The planned dose of pembrolizumab for this trial is 200 mg every 3 weeks (Q3W). Based on the totality of data generated in the Keytruda development program, 200 mg Q3W is the appropriate dose of pembrolizumab across all indications and regardless of tumour 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 tumour (inferred from physiologically based pharmacokinetic [PBPK] analysis) at 200 mg Q3W

Among the eight randomized dose-comparison studies, a total of 2262 subjects with melanoma and NSCLS were enrolled covering different disease settings (treatment naïve, previously treated, PD-L1 enriched and all-comers) and different treatment settings (monotherapy and in combination with chemotherapy). Five studies compared 2 mg/kg Q3W 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 tumour 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 tumour 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 tumour PD-1 saturation over a wide range of tumour penetration and PD-1 expression. This evaluation concluded that pembrolizumab at 200 mg Q3W achieves full PD-1 saturation in both blood and tumour.

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. A fixed-dose regimen is expected to simplify the dosing regimen (potentially reducing dosing errors), as well as be more convenient for physicians. A fixed dosing scheme will also reduce complexity in the logistical chain at treatment facilities, as well as reduce waste.

4.2.2.1 Rationale for Use of Cisplatin + 5-Fluorouracil in First Line Gastric Cancer

Systemic chemotherapy is the mainstay of treatment for advanced and metastatic gastric cancer and combination chemotherapy regimens containing cisplatin/5-fluorouracil (5-FU) for 1st line treatment have been investigated in the following randomized Phase 3 trials [32; 33].

The V325 trial [34] was the randomized Phase 3 study to compare docetaxel/cisplatin/5-FU with cisplatin/5-FU, and showed statistically significant OS time (median 9.2 months and 8.6 months, respectively, p = 0.02) PFS time (median 5.6 months and 3.7 months, respectively, p = 0.001), response rate (37% and 25%, respectively, p = 0.01) associated with docetaxel/cisplatin/5-FU. Regarding the safety, the addition of docetaxel was associated with increased Grade 3-4 neutropenia (82%, versus 57% with 5 FU/cisplatin alone), complicated neutropenia (29% vs. 12%), Grade 3-4 diarrhoea (19% vs. 8%), and Grade 3-4 lethargy (19% vs. 14%). The result of V325 supported the registration of docetaxel and docetaxel/cisplatin/5-FU as one of the standard regimen for 1st line treatment for gastric cancer. However, due in part to this increased toxicity; incorporation of docetaxel into first-line gastric cancer regimens has been limited.

The Real-2 trial [35] was a phase 3 study to compare epirubicin + oxaliplatin + 5-FU [EOF], epirubicin + cisplatin + capecitabine [ECX], epirubicin + cisplatin + 5-FU [ECF], and epirubicin + oxaliplatin + capecitabine [EOX] in advanced esophagogastric cancer. OS was significantly longer among subjects receiving EOX versus ECF (9.9 months, 9.3 months, 9.9 months, and 11.2 months for ECF, EOF, ECX, and EOX, respectively). No significant differences were observed in terms of response rate or PFS. As an outcome of the Real-2 trial, cisplatin/5-FU/epirubicin became one of the popular regimens for 1st line treatment for gastric cancer in EU. However, according to the ESMO guideline (2013), the use of triplet regimen should be limited because of increased toxicity. There are no Phase 3 trials directly comparing cisplatin/5-FU and cisplatin/5-FU/epirubicin.

ML17032 study [36] compared cisplatin/capecitabine with cisplatin/5-FU. The primary objective was to show non-inferiority in terms of PFS time. Median PFS was 5.6 months among subjects receiving cisplatin/capecitabine and 5.0 months among subjects receiving cisplatin/5-FU; median OS times were 10.5 months and 9.3 months, and ORR were 46% and 32%, in these groups respectively. Based on this study, capecitabine has been approved in combination with a platinum-based regimen for the first-line therapy of advanced gastric cancer in US and Japan.

The SPIRITS study [37] was Phase 3 trial to compare the oral fluoropyrimidine S1 plus cisplatin vs S1 in Japanese subjects. Median OS was 13 months vs 11 months. PFS was 6 months vs. 4 months; $p < 0.001$). Based on these data, S1 plus cisplatin became the most popular regimen for the first-line therapy of advanced gastric cancer in Japan.

The FLAGS trial [38] was phase 3 trial to compare the oral fluoropyrimidine S1 plus cisplatin vs 5-FU plus cisplatin in western population. The trial failed to show superiority for S1 plus cisplatin over 5-FU plus cisplatin; median OS was 8.6 months and 7.9 months, for S1/cisplatin and 5-FU/cisplatin, respectively. More toxicity of S1 and dose reduction due to AEs was observed in Western population.

In summary, platinum/fluoropyrimidine doublet regimens are the most broadly used for first-line chemotherapy regimen for advanced gastric cancer. The comparable efficacy of regimens substituting capecitabine for infused 5-fluorouracil has been directly studied in two phase III trials: the REAL-2 study and the ML17032 study. The combination of infused or oral 5-fluorouracil and cisplatin is therefore recognized worldwide as one of the standard first-line chemotherapy regimens for subjects with mGC.

4.2.3 Rationale for Endpoints

4.2.3.1 Rationale for Efficacy Endpoints

4.2.3.1.1 Primary Efficacy Endpoints

Although OS is the gold standard for a “hard endpoint” in clinical studies in the area of oncology, OS as a primary endpoint for a 1st line gastric trial with PD-1/ PD-L1 pathway inhibitors may be extremely difficult to achieve. In US/ EU, gastric cancer is a rare tumour type and most subjects have advanced or metastatic disease at the time of diagnosis. Because of the limited number of subjects in western countries and the multiple companies developing this class of drugs for gastric cancer, it is expected that there will be a high cross over rate for the chemotherapy arm subjects. Therefore, this trial will use a dual endpoint of OS and PFS. PFS is an acceptable scientific endpoint for a randomized Phase III trial to demonstrate superiority of a new antineoplastic therapy. RECIST 1.1 will be used to determine the dates of progression as this methodology is accepted by regulatory authorities. Because the treatment assignment is unblinded for pembrolizumab monotherapy, images will be read by central radiologists blinded to treatment assignment to minimize bias in the response.

4.2.3.1.2 RECIST and Immune-related RECIST

RECIST 1.1 will be adapted to account for the unique tumour response characteristics seen with treatment of pembrolizumab. Immunotherapeutic agents such as pembrolizumab may produce antitumour effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents, and can manifest a clinical response after an initial increase in tumour burden or even the appearance of new lesions. Standard RECIST 1.1 may, thus, not provide an accurate response assessment of immunotherapeutic agents such as pembrolizumab. Based on an analysis of subjects with melanoma enrolled in KEYNOTE-001 (KN001), 7% of evaluable subjects experienced delayed or early tumour pseudoprogression. Of note, subjects who had progressive disease by RECIST 1.1 but not by immune-related response criteria had longer OS than subjects with progressive disease 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 enable treatment beyond initial radiographic progression.

Immune-related RECIST (irRECIST) is RECIST 1.1 adapted to account for the unique tumour response seen with immuno-therapeutics as described in [51]. The assessment of unidimensional target lesions and response categories per irRECIST are identical to RECIST 1.1. However, Sponsor has implemented an adaptation related to new lesions, non-target and tumour burden assessment in order to confirm radiographic progression. irRECIST will be used by local site investigators to assess tumour response and progression, and make treatment decisions as well as by BICR in support of primary endpoint.

For further information on irRECIST, see Section 7.1.2.6.6.

4.2.3.2 Rationale for **Patient Reported Outcomes (PRO)**

The EORTC QLQ-C30 and EuroQoL-5D (EQ-5D) patient reported outcomes (PROs) are not pure efficacy or safety endpoints because they are affected by both disease progression and treatment tolerability.

4.2.3.2.1 EORTC QLQ-C30 and eEORTC QLQ-STO22

The EORTC QLQ-C30 is the most widely used cancer specific HRQoL instrument, which contains 30 items and measures five functioning dimensions (physical, role, cognitive, emotional, and social), three symptom items (fatigue, nausea/vomiting, pain), six single items (dyspnea, sleep disturbance, appetite loss, constipation, diarrhoea, and financial impact), and a global health and quality of life scale [39]. This instrument has been translated and validated into 81 languages and used in more than 3,000 studies worldwide.

The EORTC QLQ-STO22 is a disease-specific questionnaire developed and validated to address measurements specific to gastric cancer. It is one of multiple disease-specific modules developed by the EORTC QLG (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 22 items with symptoms of dysphagia (four items), pain or discomfort (three items), upper GI symptoms (three items), eating restrictions (five items), emotional (three items), dry mouth, hair loss, and body image.

The EORTC QLQ-C30 and EORTC QLQ-STO22 are to be completed at various time points as specified in the Trial Flow Chart, beginning with Cycle 1 until 30 days post-treatment discontinuation.

4.2.3.2.2 eEuroQoL-5D -3L

The eEuroQol-5D-3L (eEQ5D-3L) is a standardized instrument for use as a measure of health outcome. The eEQ5D-3L will provide data for use in economic models and analyses including developing health utilities or quality adjusted life years (QALYs). The five 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 three-point scale from 1 (extreme problem) to 3 (no problem). The eEQ5D-3L 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 eEQ5D-3L will always be completed by subjects first before completing the EORTC QLQ-C30 and QLQ-STO22 and is to be completed at various time points as specified in the Trial Flow Chart, beginning with Cycle 1 until 30 days post-treatment discontinuation.

4.2.3.3 Rationale for Safety Endpoints

The safety objective of this trial is to characterize the safety and tolerability of pembrolizumab monotherapy and in combination therapy in subjects with gastric or GEJ adenocarcinoma. The safety analysis will be based on subjects who experienced toxicities as defined by CTCAE criteria. Safety will be assessed by quantifying the toxicities and grades experienced by subjects who have received study treatments, including SAEs and ECIs. Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs, laboratory tests, and vital signs, Safety will be assessed by reported adverse experiences using CTCAE, Version 4.0. The attribution to drug, time-of-onset, duration of the event, its resolution, and any concomitant medications administered will be recorded. AEs will be analysed including but not limited to all AEs, SAEs, fatal AEs, and laboratory changes.

4.2.3.4 Planned Exploratory Biomarker Research

Additional biomarker research to identify factors important for pembrolizumab monotherapy and in combination therapy may also be pursued. For example, tumour and blood samples (including serum and plasma) from this trial may undergo proteomic, genomic, metabolomics, and transcriptional analyses. This research may evaluate factors important for predicting responsiveness or resistance to pembrolizumab monotherapy or combination therapy and other immunologic targets. Assays may include but are not be limited to:

Immunohistochemistry

PD-L1 expression in tumour tissue will be characterized by immunohistochemistry to explore the relationship between PD-L1 expression and response to treatment with pembrolizumab monotherapy or combination therapy. Other exploratory biomarkers (eg PD-1 expression, markers of T-cell phenotype) may also be evaluated.

Transcriptional Analyses

Messenger RNA (mRNA) expression profiling in archival material (biopsy specimens, peripheral blood) will be completed using the NanoString platform to assess expression of approximately 700 genes and attempt to define a gene set critical for clinical response to pembrolizumab monotherapy or combination. The hypothesis to be tested is that pembrolizumab induces responses in tumours that reflect an inflamed/ immune phenotype based on gene expression signatures capturing PD-L1 & interferon-gamma transcriptional programs. Global profiling will also be pursued. Expression of individual genes related to the immune system may also be evaluated such as immune signatures and critical cytokines (eg, IL-10). MicroRNA profiling may also be pursued in serum samples.

Proteomic analysis

In addition to expression on the tumour tissue, PD-L1 can be shed from tumour and released into the blood. Enzyme-linked immunoassay can measure PD-L1 in serum and correlate this expression with response to pembrolizumab monotherapy or combination therapy, as well as levels of PD-L1 IHC or protein in the tumour. Blood would be a less invasive component from which to measure PD-L1 protein biomarker. In addition to this specific protein biomarker, both tissue and blood derivatives can be subjected to proteomic profiling studies using a variety of platforms that could include but are not limited to immunoassay, Liquid chromatography/Mass Spectrometry. This approach could identify novel protein biomarker that could aid in subject selection for pembrolizumab monotherapy or combination therapy.

Gene Analyses

The application of new technologies, such as next generation sequencing, has provided scientists the opportunity to define certain tumour types at the genetic level as being ‘hypermutated’ or can detect the presence of specific T-cell clones within the tumour microenvironment or in the peripheral blood. There is a potential that the hypermutated state and/or increased T-cell clonality may correlate with response to pembrolizumab monotherapy or combination therapy, and/or that the converse, ‘hypomutated’ state or lack of dominant T-cell clones may correlate with non-response.

In addition, understanding genetic determinants of drug response is an important endeavour during medical research. 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 subject population. This research contributes to understanding genetic determinants of efficacy and safety associated with the treatments in this study.

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

4.2.3.5 Future Biomedical Research

The Sponsor will conduct Future Biomedical Research on specimens collected 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.

Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol (as part of the main trial) and will only be conducted on specimens from appropriately consented subjects. The objective of collecting specimens for Future Biomedical Research is to explore and identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments. For instance, exploratory pharmacogenetic (PGt) studies may be performed if significant Pharmacokinetic/Pharmacodynamic (PK/PD) relationships are observed or adverse events are identified. Genomic markers of disease may also be investigated. Such retrospective pharmacogenetic studies will be conducted with appropriate biostatistical design and analysis and compared to PK/PD results or clinical outcomes. Any significant PGt relationships to outcome would require validation in future clinical trials. The overarching goal is to use such information to develop safer, more effective drugs/vaccines, and/or to ensure that subjects receive the correct dose of the correct drug/vaccine at the correct time. The details of this Future Biomedical Research sub-trial are presented in Section 12.2 - Collection and Management of Specimens for Future Biomedical Research. Additional informational material for institutional review boards/ethics committees (IRBs/ERCs) and investigational site staff is provided in Section 12.3.

4.3 Benefit/Risk

Subjects in clinical trials generally cannot expect to receive direct benefit from treatment during participation, as clinical trials are designed to provide information about the safety and effectiveness of an investigational medicine.

Additional details regarding specific benefits and risks for subjects participating in this clinical trial may be found in the accompanying Investigators Brochure (IB) and Informed Consent documents.

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 subjects (KN001), which led to USFDA approval in September 2014, and in a randomized comparison to chemotherapy (KEYNOTE-002 [KN002]– detailed in the IB). Additional potential benefits are addressed in section 4.1.3.1

which details responses of KN012 trial; a multi-cohort Phase Ib study of which one cohort enrolled subjects with recurrent or metastatic gastric or GEJ adenocarcinoma that expressed PD-L1 (≥1% by immunohistochemistry). Although two-thirds of subjects had received at least two prior therapies for advanced disease, pembrolizumab monotherapy achieved an interim ORR of 33.3% by RECIST v.1.1 per investigator review (95% confidence interval (CI) (19.1%, 50.2%); all partial responses). The interim disease control rate (DCR) was 41% (95% CI (25.6%, 57.9%), and the interim median duration of response was 24 weeks (range 8+ to 33+ weeks).

In KN012 the most common AEs included fatigue (17.9%), decreased appetite (12.8%), hypothyroidism (12.8%), and arthralgia (10.3%). Three Grade 3 AEs were observed, one each for peripheral sensory neuropathy, fatigue, and decreased appetite. In addition, one Grade 4 pneumonitis and one Grade 5 hypoxia were reported.

An early safety analysis will be performed to evaluate the safety of each treatment arm. This interim safety analysis will occur when at least10 subjects from each arm (30 total subjects) have completed at least 1 cycle of treatment. The safety data will be submitted to an external DMC.

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

Male/Female subjects with locally advanced unresectable or metastatic gastric or GEJ adenocarcinoma 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/assent for the trial. The subject may also provide consent/assent for Future Biomedical Research. However, the subject may participate in the main trial without participating in Future Biomedical Research.

2. Be ≥ 18 years of age on day of signing informed consent (or acceptable age according to local regulations, whichever is older).

3. Have a performance status of 0 or 1 on the Eastern Cooperative Oncology Group (ECOG) Performance Scale within 3 days prior to the first dose of trial treatment.

4. Have histologically or cytologically confirmed diagnosis of locally advanced unresectable or metastatic gastric or GEJ adenocarcinoma.

5. Be HER2/neu negative and PD-L1 positive.

6. Have measurable disease as defined by RECIST 1.1 as determined by investigator assessment. Tumour lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions.

    a. Note: The exact same image acquisition and processing parameters should be used throughout the study.

7. Have provided tumour tissue sample deemed adequate for PD-L1 biomarker analysis. Refer to Section 7.1.1.2.1 for details

    a. Notification of eligibility must be received prior to randomization.

    b. Additional samples may be required if adequate tissue is not provided.

8. Female subjects of childbearing potential must have a negative urine or serum pregnancy test within 72 hours prior to receiving the first dose of study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
9. Female subjects of childbearing potential (Section 5.7.2) 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.

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

10. Male subjects of childbearing potential (Section 5.7.2) 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 therapy.

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

11. Demonstrate adequate organ function as defined in Table 2. All screening labs should be performed within 10 days of treatment initiation.

Table 2 Adequate Organ Function Laboratory Values

System	Laboratory Value
Haematological	
Absolute neutrophil count (ANC)	≥1,500 /mcL
Platelets	≥100,000 / mcL
Haemoglobin	≥9 g/dL – transfusion is acceptable if necessary to increase haemoglobin levels
Renal	
Creatinine **OR** Measured or calculated[a] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 X upper limit of normal (ULN) **OR** ≥60 mL/min for subject with creatinine levels > 1.5 X institutional ULN Cisplatin product label should be followed for acceptable creatinine clearance rates for subjects in Arms 2 and 3 (combination treatment)
Hepatic	
Total bilirubin	≤ 1.5 X ULN **OR** Direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 X ULN **OR** ≤ 5 X ULN for subjects with liver metastases
Albumin	≥ 2.5 g/dL
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT) Activated Partial Thromboplastin Time (aPTT)	≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants ≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants

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

5.1.3 Subject Exclusion Criteria

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

1. Has squamous cell or undifferentiated gastric cancer.

2. Has had previous therapy for locally advanced, unresectable or metastatic gastric/GEJ cancer. Subjects may have received prior neoadjuvant or adjuvant therapy as long as it was completed at least 6 months prior to randomization.

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 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.

5. Has a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin that has undergone potentially curative therapy or in situ cervical cancer.

6. Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging at least four weeks prior to the first dose of trial treatment and neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to trial treatment. This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability.

7. 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, etc.) is not considered a form of systemic treatment.

8. 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 the first dose of trial drug.

9. Has a history of (non-infectious) pneumonitis that required steroids or current pneumonitis

10. Has an active infection requiring systemic therapy.

11. Has a history or current evidence of any condition (eg known deficiency of the enzyme dihydropyrimidine dehydrogenase [DPD]), therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.

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

13. 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 trial treatment.

14. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent.

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

16. Has known active Hepatitis B (eg, HBsAg reactive) or Hepatitis C (eg, HCV RNA [qualitative] is detected).

17. Is currently participating in and receiving study therapy or has participated in a trial of an investigational agent or has used an investigational device within 4 weeks prior to the first dose of trial treatment.

18. Has received a live vaccine within 30 days prior to the first dose of trial drug.

Note: Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, Bacillus Calmette-Guérin (BCG), and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines, and are not allowed.

5.2 Trial Treatment(s)

The treatments to be used in this trial are outlined below in Table 3.

Table 3 Trial Treatments

Drug	Dose	Dose Frequency	Route of Administration	Regimen/Treatment Period/Vaccination Regimen	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*	80 mg/m^2	Q3W	IV infusion	Day 1 of each cycle	Comparator regimen and combination agent
5-FU**	800 mg/m^2	Q3W	IV infusion	Continuous Days 1-5 (120 hours) of each cycle	Comparator regimen and combination agent
Capecitabine**	1000 mg/m^2 BID	Q3W	Oral	D1-14	Comparator regimen and combination agent

* Duration of cisplatin treatment may be capped at 6 cycles as per local country guidelines, however treatment with 5-FU/capecitabine may continue per protocol.

**Although use of 5-FU infusion is preferred, capecitabine 1000 mg/m2 bid D1-14 Q3W may be permitted according to local guideline. Investigator decision regarding the type of comparator used (5-FU or capecitabine) should be determined prior to randomization in the trial.

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

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

All supplies indicated in Table 3 above will be provided centrally by the Sponsor or locally by the trial site, subsidiary or designee, depending on local country operational or regulatory requirements.

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

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

5.2.1 Dose Selection/Modification

5.2.1.1 Dose Selection (Preparation)

The rationale for selection of 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, 5-FU and capecitabine should follow the local product label. The body surface area (BSA) in m^2 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 capecitabine) or pembrolizumab alone in the combination arms and use a stepwise dose reduction according to Table 4 to Table 8. 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.

Pembrolizumab/placebo dose reductions are not permitted. Pembrolizumab/placebo treatment may be interrupted or discontinued due to toxicity. 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, please follow the most conservative dose adjustment recommended (dose reduction appropriate to the most severe toxicity). Subjects who require a 3rd 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 three agents, chemotherapy should be reduced, interrupted or discontinued; pembrolizumab/placebo should be interrupted or discontinued according to the recommended dose modifications. If a decision is made to discontinue combination chemotherapy due to treatment related AE(s), the subject can be unblinded after discussion with sponsor to identify study treatment. Subjects receiving pembrolizumab therapy may have both the cisplatin and 5-FU or capecitabine discontinued and continue on pembrolizumab alone, while subjects on combination with placebo (arm 3) may discontinue from study treatment.

The Common Terminology Criteria for Adverse Events version 4.0 (CTCAE 4.0) must be used to grade the severity of AEs. All dose modifications should be based on the AE requiring the greatest dose modification. Dose modifications are detailed in Table 4 through Table 8. Exceptional circumstances to following the dose modification tables below may be considered after consultation with the Sponsor.

Table 4 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	40 mg/ m^2	Discontinue
5-FU **Capecitabine**	800 mg/ m^2 1000mg/ m^2 BID	600 mg/ m^2 750mg/ m^2 BID	400 mg/ m^2 500mg/ m^2 BID	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 label or local guidelines for cisplatin and 5-FU, (or capecitabine) 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 AEs associated with pembrolizumab

Adverse events associated with pembrolizumab exposure may represent an immunologic aetiology. 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 aetiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, 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 5.

Table 5 Dose Modification and Toxicity Management Guidelines for Immune-related AEs Associated With pembrolizumab

General instructions:

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

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

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

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

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

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

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 6.

Table 6 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 hrs	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within 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 drug treatment	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of _____ with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of analgesic).
Grades 3 or 4 Grade 3: Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (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 drug treatment.**	No subsequent dosing
Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE) at http://ctep.cancer.gov		

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-FU

Please refer to criteria for cisplatin and 5-FU (or capecitabine) dose modification included in Table 7 and Table 8, respectively.

Table 7 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
Haematologic[3]	Neutropenia	3[1]	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[1]	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[1]	Toxicity resolves to Grade 0-1	Reduce by 1 DL	Toxicity does not resolve within 4 weeks of last infusion or if >2 Dose Level reductions exceeded
		4[1]	n/a	Discontinue	Permanently discontinue Cisplatin
	Thrombocytopenia	3-4[1]	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

Category	Toxicity	Hold Cisplatin Treatment for Grade	Timing for Restarting Cisplatin Treatment	Dose for Restarting Cisplatin Treatment	Discontinue Cisplatin
Non-haematologic	Creatinine Increased	2	Toxicity resolves to Grade 0-1	Reduce by 1 DL	Toxicity does not resolve within 4 weeks of last infusion or if >2 Dose Level reductions exceeded
		3-4[1]	Toxicity resolves to Grade 0-1	Reduce by 1 DL	Toxicity does not resolve within 4 weeks of last infusion or if >2 Dose Level reductions exceeded
	Ototoxicity or Sensory neuropathy	3-4[1]	Toxicity resolves to Grade 0-1	Reduce by 1 DL	Toxicity does not resolve within 4 weeks of last infusion or if >2 Dose Level reductions exceeded
	All other non-haematologic toxicities[2]	3-4[1]	Toxicity resolves to Grade 0-1	Reduce by 1 DL	Toxicity does not resolve within 4 weeks of last infusion or if >2 Dose Level reductions exceeded
	Laboratory Adverse Events	4[1]	Toxicity resolves to Grade 0-1	Reduce by 1 DL	Toxicity does not resolve within 4 weeks of last infusion or if >2 Dose Level reductions exceeded

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

2 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 0-1 within 12 weeks of the last dose.

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

Table 8 Dose Modification Guidelines for 5-Fluorouracil (5-FU) /Capecitabine Drug-Related Adverse Events

Category	Toxicity	Hold 5-FU/ Capecitabine Treatment for Grade	Timing for Restarting 5-FU/ Capecitabine Treatment	Dose for Restarting 5-FU/ Capecitabine Treatment	Discontinue 5-FU/Capecitabine
Haematologic[3]	Neutropenia	3[1]	Neutrophil count resolves to >1,000/mm^3	No Reduction *consider G-CSF	Toxicity does not resolve within 4-5 weeks of last infusion or if > 2 Dose Level reductions exceeded
		4[1]	Neutrophil count resolves to >1,000/mm^3	Reduce by 1 DL *consider G-CSF	Toxicity does not resolve within 4-5 weeks of last infusion or if > 2 Dose Level reductions exceeded
	Febrile Neutropenia	3[1]	Toxicity resolves to Grade 0-1	Reduce by 1 DL	Toxicity does not resolve within 4-5 weeks of last infusion or if > 2 Dose Level reductions exceeded
		4[1]	n/a	Discontinue	Permanently discontinue
	Thrombocytopenia	3-4[1]	Platelet count resolves to >75,000/mm^3	Reduce by 1 DL	Toxicity does not resolve within 4-5 weeks of last infusion or if > 2 Dose Level reductions exceeded
Non-haematologic	Diarrhea, Mucositis, or Hand-foot syndrome	2-3	Toxicity resolves to Grade 0-1	Reduce by 1 DL	Toxicity does not resolve within 4-5 weeks of last infusion or if > 2 Dose Level reductions exceeded
		4	N?A	Discontinue	Permanently discontinue
	All other non-hematologic toxicities[2]	3-4[1]	Toxicity resolves to Grade 0-1	Reduce by 1 DL	Toxicity does not resolve within 4-5 weeks of last infusion or if > 2 Dose Level reductions exceeded
	Laboratory Adverse Events	4[1]	Toxicity resolves to Grade 0-1	Reduce by 1 DL	Toxicity does not resolve within 4-5 weeks of last infusion or if > 2 Dose Level reductions exceeded

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

2 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 0-1 within 12 weeks of the last dose.

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

5.2.2 Second Course Phase (Retreatment Period)

All subjects who stop trial treatment with SD or better may be eligible for up to an additional 17 cycles (approximately 1 year) of pembrolizumab treatment if they progress after stopping trial treatment from the initial treatment phase. This retreatment is termed the Second Course Phase of this trial and is only available if the trial remains open and the subject meets the following conditions:

Either

- Stopped initial treatment with trial treatment after attaining an investigator-determined confirmed CR based on RECIST 1.1, and
  - Was treated with at least 8 cycles of trial treatment before discontinuing treatment, and
  - Received at least 2 treatments with pembrolizumab beyond the date when the initial CR was declared

OR

- Had SD, PR, or CR and stopped trial treatment after completion of 35 administrations (approximately 2 years) of trial treatment for reasons other than disease progression or intolerability

AND

- Experienced an investigator-determined radiographic disease progression by RECIST 1.1 after stopping initial treatment, and
  - Upon unblinding at the time of centrally verified disease progression were found to have received pembrolizumab, and
  - No new anticancer treatment was administered after the last dose of trial treatment, and
  - The subject meets all of the safety parameters listed in the inclusion criteria and none of the safety parameters listed in the exclusion criteria, and
  - The trial is ongoing

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

5.2.3 Timing of Dose Administration

Study treatment in all arms will begin on Day 1 of each 3-week dosing cycle after all procedures/assessments have been completed as detailed on the Trial Flow Chart (Section 6.0). 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.

For subjects randomized to the combination arms treatment will be administered in the order presented below:

- Pembrolizumab or placebo infusion is administered first followed by the cisplatin infusion and then 5-FU infusion (or capecitabine).

Treatment may continue with pembrolizumab+chemotherapy or placebo+chemotherapy until documented confirmed disease progression, unacceptable AE(s), 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, 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 (ie 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 subjects cannot restart study medication within 3 weeks. The reason for interruption should be documented in the subject's study record.

5.2.3.1 Pembrolizumab

Regardless of clinical benefit, subjects may only receive 35 administrations (approximately 2 years) with study treatment. 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 (ie, infusion time is 30 minutes: -5 min/+10 min).

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

5.2.3.2 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).

5.2.3.3 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 completion of all procedures and assessments are completed according to the Trial Flow Chart in Section 6.0. Duration of cisplatin treatment may be capped at 6 cycles as per local country guidelines.

5.2.3.4 5-Fluorouracil (5-FU)

5-FU 800 mg/m^2/day will be administered as a continuous IV infusion from Day 1 to Day 5 (120 hours) of each treatment cycle, after completion of all procedures and assessments according to the Trial Flow Chart in Section 6.0.

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

5.2.3.5 Capecitabine

Although use of 5-FU infusion is preferred, capecitabine 1000 mg/m^2 bid Day1 to Day 14 Q3W may be permitted according to local guidelines at the Investigator's discretion. Investigator decision regarding the type of comparator (5-FU or capecitabine) used should be determined prior to randomization in the trial. The evening dose of capecitabine should be taken approximately 12 hours after the morning dose and should be taken with food, or within 30 minutes after food/meal, with approximately 200 ml of water. Please refer to the product label for additional guidance on administration procedures for capecitabine. **Note:** If subject is enrolled later in the day, it is acceptable for only 1 dose taken on Day 1, and BID dosing can resume on Days 2-14 and the final dose will be taken in the morning of D15.

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

5.2.4 Trial Blinding/Masking

This study is partially blinded:

Treatment Arm 1: Pembrolizumab monotherapy, the subject, the trial site personnel, the Sponsor and/or designee will not be blinded to this treatment arm since only one type of study medication will be administered in this arm.

Treatment Arm 2 and Treatment Arm 3: Pembrolizumab or placebo treatment in the combination chemotherapy arms (pembrolizumab+chemotherapy and placebo+chemotherapy, respectively) is blinded to the subject, study site personnel and SPONSOR personnel.

Pembrolizumab monotherapy (Arm 1) and pembrolizumab/placebo in the combination chemotherapy arms (Arms 2 & 3) will be prepared in a blinded fashion by an assigned unblinded pharmacist or qualified trial site personnel. The investigator or qualified site personnel will administer pembrolizumab/placebo to subjects in Treatment Arms 2 and 3 in a blinded fashion, therefore subjects, site personnel and sponsor personnel are blinded to pembrolizumab/placebo treatment for these 2 arms.

Even though the trial is only partially blinded (ie treatment arm 1 is open label), the following measures will be taken to help maintain internal blinding: 1) imaging data are

centrally reviewed and the central reviewer is blinded to subject treatment assignment; 2) allocation schedule is blinded in the database preventing aggregate analysis.

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

5.3 Randomization or Treatment Allocation

Randomization will occur centrally using an interactive voice response system / integrated web response system (IVRS/IWRS). There are 3 treatment arms. Subjects will be assigned randomly in a 1:1:1 ratio to pembrolizumab monotherapy, pembrolizumab+chemotherapy, or placebo+chemotherapy, respectively. Although use of 5-FU infusion is preferred, capecitabine 1000 mg/m^2 bid Day1 to Day 14 Q3W may be permitted according to local guidelines at the Investigator's discretion. Investigator decision regarding the type of comparator used (5-FU or capecitabine) should be determined prior to randomization in the trial. Documentation of the comparator to be used (5-FU or capecitabine) will be documented in IVRS/IWRS prior to randomization.

5.4 Stratification

Randomization will be stratified according to the following factors:

1. Geographic region (Europe [including Israel]/North America/Australia vs. Asia [including East Asia, South Korea, Hong Kong, Taiwan, and South East Asia Malaysia, Thailand, Singapore, Japan] vs. Rest of the World (including South America)

2. Disease Status (locally advanced unresectable vs metastatic disease)

3. Fluoropyrimidine treatment (5-FU vs capecitabine)

5.5 Concomitant Medications/Vaccinations (Allowed & Prohibited)

5.5.1 Acceptable Concomitant Medications

All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the CRF 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 CRF.

All concomitant medications received during the trial through 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered after 90 days after the last dose of trial treatment should be recorded for SAEs and ECIs as defined in Section 7.2.

5.5.2 Prohibited Concomitant Medication

Subjects are prohibited from receiving the following therapies during Screening to the end of Treatment (including retreatment for post-CR relapse) of this trial:

- Antineoplastic systemic chemotherapy or biological therapy not specified in the protocol
- Immunotherapy not specified in this protocol
- Investigational agents other than pembrolizumab
- Radiation therapy; palliative radiation therapy to a symptomatic lesion (eg bony metastasis), or to the brain may be permitted after consultation with the 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, chicken pox, yellow fever, rabies, BCG, and typhoid (oral) vaccine. The killed virus vaccines used for seasonal influenza vaccines for injection are allowed; however live attenuated intranasal influenza vaccines (eg Flu - Mist®) are not allowed.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an AE of suspected immunologic aetiology or cisplatin supportive care. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor (eg, for control of acute asthma symptoms).
- For subjects randomized to 5-FU or capecitabine:
    - Brivudine, Sorivudine analogues, and other inhibitors of the enzyme dihydropyrimidine dehydrogenase (DPD)
- For subjects randomized to cisplatin:
    - Phenytoin should not be started with cisplatin therapy.

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

Concomitant Medications to be used with caution

- Cimetidine, Metronidazole and interferons may increase levels of 5-FU.
    - Subjects who are taking Phenytoin in conjunction with 5-Fluorouracil should be examined regularly due to a potential elevation in Phenytoin plasma levels.

Hepatotoxic effects (rise in alkaline phosphatase, transaminase or bilirubin levels) are commonly observed under the treatment with 5-Fluorouracil and Levamisole.

The Exclusion Criteria describes other medications which are prohibited during the treatment phase of this trial.

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 aetiology are outlined below and in greater detail in Section 5.2.1.2.1 Table 5 . Where appropriate, these guidelines include the use of oral or intravenous treatment with corticosteroids as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab.

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event. Suggested conditional procedures, as appropriate, can be found in Section 5.2.1.2.1..

- **Pneumonitis**:
    - For **Grade 2 events**, treat with systemic corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. For recurrent Grade 2 pneumonitis, please refer to Table 5 for guidance.
    - For **Grade 3-4 events**, immediately treat with intravenous steroids. Administer additional anti-inflammatory measures, as needed.
    - Add prophylactic antibiotics for opportunistic infections in the case of prolonged steroid administration.
- **Diarrhea/Colitis**:

  Subjects should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhoea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus).

- All subjects who experience diarrhoea/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. For Grade 2 or higher diarrhoea, consider GI consultation and endoscopy to confirm or rule out colitis.

- For **Grade 2 diarrhoea/colitis** that persists greater than 3 days, administer oral corticosteroids.

- For **Grade 3 or 4 diarrhoea/colitis** that persists > 1 week, treat with intravenous steroids followed by high dose oral steroids.

- When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

- **Type 1 diabetes mellitus (if new onset, including diabetic ketoacidosis [DKA]) or ≥ Grade 3 Hyperglycaemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA)**

  - For **T1DM** or **Grade 3-4** Hyperglycaemia

    - Insulin replacement therapy is recommended for Type I diabetes mellitus and for Grade 3-4 hyperglycaemia associated with metabolic acidosis or ketonuria.

    - Evaluate subjects with serum glucose and a metabolic panel, urine ketones, glycosylated haemoglobin, and C-peptide.

- **Hypophysitis**:

  - For **Grade 2** events, treat with corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

  - For **Grade 3-4** events, treat with an initial dose of IV corticosteroids followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

- **Hyperthyroidism or Hypothyroidism**:

  Thyroid disorders can occur at any time during treatment. Monitor subjects for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders.

- **Grade 2** hyperthyroidism events (and **Grade 2-4** hypothyroidism):
  - In hyperthyroidism, non-selective beta-blockers (eg propranolol) are suggested as initial therapy.
  - In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyronine, is indicated per standard of care.
- **Grade 3-4** hyperthyroidism
  - Treat with an initial dose of IV corticosteroid followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

- **Hepatic**:
  - For **Grade 2** events, monitor liver function tests more frequently until returned to baseline values (consider weekly).
    - Treat with IV or oral corticosteroids
  - For **Grade 3-4** events, treat with intravenous corticosteroids for 24 to 48 hours.
  - When symptoms improve to Grade 1 or less, a steroid taper should be started and continued over no less than 4 weeks.

- **Renal Failure or Nephritis**:
  - For **Grade 2** events, treat with corticosteroids.
  - For **Grade 3-4** events, treat with systemic corticosteroids.
  - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

Management of Infusion Reactions: Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Table 9 below shows treatment guidelines for subjects who experience an infusion reaction associated with administration of pembrolizumab (MK-3475).

Table 9 Infusion Reaction Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs.	**Stop Infusion and monitor symptoms.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (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 trial treatment administration.**	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab (MK-3475) with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).
Grades 3 or 4 Grade 3: Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilator support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **Subject is permanently discontinued from further trial treatment administration.**	No subsequent dosing
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.		

5.6.2 Supportive Care Guidelines for Cisplatin

Prevention and/or treatment of nausea and vomiting should be managed with:

1. IV EMEND (fosaprepitant) 150 mg IV or oral EMEND (aprepitant) 3-day pack 125 mg day 1, 80 mg day 2, 80 mg day 3

2. Plus Aloxi (Palonosetron) 0.25 mg IV

Nausea may also be managed with:

1. Zofran (Ondansetron) 8 mg twice a day

2. Or Compazine (Prochlorperazine) 10 mg 3-4 times per day

Additionally, use of steroids for cisplatin associated anti-emetic support is allowed and is to follow the NCCN or institutional guidelines.

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

5.6.3 Supportive Care Guidelines for 5-Fluorouracil

Please refer to the product label or local standards of care for fluorouracil supportive measures.

5.6.4 Supportive Care Guidelines for Capecitabine

Please refer to the product label or local standards of care for capecitabine 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 diarrhoea, nausea or vomiting.

5.7.2 Contraception

Pembrolizumab may have adverse effects on a foetus 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 1 of the following criteria:

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

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

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

- Female and male subjects of reproductive potential must agree to avoid becoming pregnant or impregnating a partner, respectively, while receiving trial drug and for 120 days after the last dose of trial drug by complying with 1 of the following:

- Practice abstinence† from heterosexual activity.

†Abstinence (relative to heterosexual activity) can be used as the sole method of contraception if it is consistently employed as the subject's preferred and usual lifestyle and if considered acceptable by local regulatory agencies and European Research Councils (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.

Acceptable methods of contraception are[a]:

    - Single method (1 of the following is acceptable):

    - Intrauterine device (IUD)

    - Vasectomy of a female subject's male partner

    - Contraceptive rod implanted into the skin

- Combination method (requires use of 2 of the following):

    - Diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide)

    - Cervical cap with spermicide (nulliparous women only)

- Contraceptive sponge (nulliparous women only)
- Male condom or female condom (cannot be used together)
- Hormonal contraceptive: oral contraceptive pill (estrogen/progestin pill or progestin-only pill), contraceptive skin patch, vaginal contraceptive ring, or subcutaneous contraceptive injection

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

Subjects should be informed that taking the trial medication may involve unknown risks to the foetus (unborn baby) if pregnancy were to occur during the trial. In order to participate in the trial subjects of childbearing potential must adhere to the contraception requirement (described above) from the day of study medication initiation (or 14 days prior to the initiation of trial medication for oral contraception) throughout the study period up to 120 days after the last dose of trial medication. If there is any question that a subject of childbearing potential will not reliably comply with the requirements for contraception, that subject should not be entered into the trial.

5.7.3 Use in Pregnancy

If a subject inadvertently becomes pregnant while on treatment with pembrolizumab 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 foetus 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.

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 breast-feeding are not eligible for enrolment. Specific additional information follows for individual agents used in this trial.

5.7.4.1 Pembrolizumab

It is unknown whether pembrolizumab is excreted in human milk.

5.7.4.2 Cisplatin

Cisplatin has been reported to be found in human milk; subjects receiving Cisplatin injection should not breast-feed.

5.7.4.3 5-Fluorouracil

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

5.7.4.4 Capecitabine

Lactating mice given a single oral dose of capecitabine excreted significant amounts of capecitabine metabolites into the milk. It is not known whether this drug is excreted in human milk. Subjects receiving capecitabine should not breast-feed.

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 trial will still continue to participate in the trial as specified in Section 6.0 - Trial Flow Chart and Section 7.1.5.3 – 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 disease progression outlined in Section 7.1.5 (exception if the Sponsor approves treatment continuation).
- Unacceptable adverse experiences as described in Section 7.2.

- Any progression or recurrence of any malignancy, or any occurrence of another malignancy that requires active treatment
- Intercurrent illness other than another malignancy as noted above that prevents further administration of treatment
- Recurrent Grade 2 pneumonitis
- A confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements
- Investigator's decision to withdraw the subject.
- Completed 35 administrations (approximately 2 years) of treatment.

Note: 35 administrations of study medication are calculated from the date of first dose. Subjects who stop study medication after 35 administrations may be eligible for up to 17 additional study treatments if they progress after stopping study treatment provided they meet the requirements detailed in Section 7.1.2.6.4.

- Discontinuation of treatment may be considered for subjects who have attained a confirmed complete response (CR) and have been treated for at least 8 cycles (at least 24 weeks), receiving 2 cycles of the combination including 2 doses of pembrolizumab and at least 80% of the planned doses of cisplatin, 5-Fluotouracil or capecitabine] beyond the date when the initial CR was declared.

  Subjects who stop [pembrolizumab or the combination] with stable disease (SD), partial response (PR), or CR, may be eligible for up to 1 year (17 cycles) of [pembrolizumab or additional combination therapy] if they experience disease progression after stopping [pembrolizumab or combination trial treatment]. This retreatment is termed the Second Course Phase (Retreatment) and is described in detail in Section 5.2.2.

- Administrative reasons

The End of Treatment and Follow-up visit procedures are listed in Section 6.0 (Protocol Flow Chart) and Section 7.1.5 (Visit Requirements). After the end of treatment, each subject will be followed for 30 days for AE monitoring (SAEs and ECIs will be collected for 90 days after the end of treatment or 30 days after the end of treatment if the subject initiates new anticancer therapy, whichever occurs first, as described in Section 7.2.3.1). Subjects who discontinue for reasons other than PD will have post-treatment follow-up for disease status until disease progression, initiating a non-study cancer treatment, withdrawing consent or becoming lost to follow-up. After documented disease progression each subject will be followed by telephone for OS until death, withdrawal of consent, or the end of the study, whichever occurs first.

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.

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.

5.9 Subject Replacement Strategy

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

5.10 Beginning and End of the Trial

The overall trial begins when the first subject signs the informed consent form. The overall trial ends when the last subject completes the last study-related phone-call or visit, discontinues 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

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. In addition, further recruitment in the trial or at (a) particular trial site(s) may be stopped due to insufficient compliance with the protocol, Good Clinical Practice (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

6.1 Initial Treatment Phase

6.1.1 Treatment Arm 1: Pembrolizumab Monotherapy

Trial Period:	Screening Phase		Treatment Cycles[a]						End of Treatment	Post-Treatment		
Treatment Cycle	Tumour Tissue collection/submission	Screening	1	2	3	4	5	Cycle 6 and beyond	Last Dose	Safety Follow-up	Follow Up Visits[b]	Survival Follow-up[c]
									At time of treatment discon	30 days post discontinuation	Every 6 weeks post discontinuation	Every 12 weeks
Scheduling Window (Days)[d]:	-28 to -1	-21 to -1		± 3	± 3	± 3	± 3	± 3	± 3	± 7	± 7	± 7
Administrative Procedures												
Informed Consent[e]	X											
Informed Consent for Future Biomedical Research[f]	X											
Inclusion/Exclusion Criteria		X										
Subject Identification Card		X										
Demographics and Medical History		X										
Prior and Concomitant Medication Review[g]		X	X	X	X	X	X	X	X	X		
Clinical Procedures/Assessments												
Review Adverse Events[h]	X	X	X	X	X	X	X	X	X	X	X	
ePROs (HRQoL Measures)[i]			X	X	X	X	X[i]		X	X		
12-Lead ECG (Local)		X										
Full Physical Examination		X							X			
Directed Physical Examination			X	X	X	X	X	X				
Vital Signs and Weight[j]		X	X	X	X	X	X	X	X			
ECOG Performance Status[n]		X	X	X	X	X	X	X	X			
Post-study Anticancer Therapy Status											X	X
Survival Status[c]			←	—	—	—	—	—	—	—	→	X
Trial Treatment Administration												
Pembrolizumab[k]			X	X	X	X	X	X				
Laboratory Procedures/Assessments: Analysis performed by LOCAL												

Trial Period:	Screening Phase		Treatment Cycles[a]						End of Treatment	Post-Treatment		
Treatment Cycle	Tumour Tissue collection/submission	Screening	1	2	3	4	5	Cycle 6 and beyond	Last Dose	Safety Follow-up	Follow Up Visits[b]	Survival Follow-up[c]
									At time of treatment discon	30 days post discontinuation	Every 6 weeks post discontinuation	Every 12 weeks
Scheduling Window (Days)[d]:	-28 to -1	-21 to -1		± 3	± 3	± 3	± 3	± 3	± 3	± 7	± 7	± 7
laboratory												
Pregnancy Test – Serum or Urine[l]		X	X	X	X	X	X	X		X		
PT/INR and aPTT[m]		X										
CBC with Differential[n]		X		X	X	X	X	X	X	X		
Chemistry Panel[n]		X		X	X	X	X	X	X	X		
Urinalysis[n]		X										
T3(or Free T3), FT4 and TSH[n]		X		X		X		X		X		
Serum carcinoembryonic antigen (CEA)[o]		X			X		X	X[o]				
Serum CA19-9[o]		X			X		X	X[o]				
Laboratory Procedures/Assessments: Analysis performed by CENTRAL laboratory												
Blood for Genetics[p]			X									
Correlative Blood Samples (DNA)[q]			X	X	X				X			
Correlative Blood Samples (RNA)[q]			X	X	X				X			
Correlative Blood Samples (plasma)[q]			X									
Correlative Blood Samples (serum)[q]			X									
Efficacy Measurements												
Tumour Imaging[r]		X			X		X	X	X[s]		X[s]	
Tumour Tissue Collection												
Archival and/or Newly Obtained Tissue Collection[t]	X								X			

a. Unless otherwise specified, assessments/procedures are to be performed on Day 1 and prior to the first dose of treatment for each cycle unless otherwise specified.
b. In subjects who discontinue study therapy without documented disease progression, every effort should be made to continue monitoring their disease status by radiologic imaging every 6 weeks (± 7 days) until (1) the start of new anti-cancer treatment, (2) disease progression as assessed by the central imaging vendor, (3) death, or (4) the end of the study, whichever occurs first.
c. After documented local site assessed disease progression or the start of new anticancer treatment; contacts are approximately every 12 weeks by telephone. 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).
d. Unless otherwise specified, the window for each visit is ± 3 days. Cycle 1 treatment should be given within 3 days of randomization.
e. Written consent must be obtained prior to performing any protocol specified 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 (eg, within 21 days prior to the first dose of trial treatment). Screening number will be assigned when the study informed consent is signed.
f. Signing the informed consent for future biomedical research (FBR) sample is optional. Detailed instructions for the collection and management of specimens for FBR are provided in the Procedures Manual and Section 12.2 of this protocol.
g. Prior medications – Record all medications taken within 30 days of first dose. Concomitant medications – Enter new medications started during the trial through the Safety Follow-up visit. Record all medications taken for SAEs as defined in Section 7.2.
h. Record all AEs occurring within 30 days after the last dose of trial treatment. Report all SAEs (related and unrelated to trial treatment) and ECIs occurring up until 90 days after the last dose of trial treatment or 30 days after the end of treatment if the subject initiates new anticancer therapy, whichever occurs first. Afterwards, report only SAEs and ECIs that are related to trial treatment.
i. It is strongly recommended that electronic Patient Reported Outcomes (ePROs) are administered prior to drug administration, adverse event evaluation and disease status notification starting with the EQ5D-3L, followed by EORTC QLQ-C30, and EORTC QLQ-ST022; an exception to this recommendation may occur at the treatment discontinuation visit where subjects may have already been notified of their disease status or an AE evaluation is known prior to them arriving to the clinic. All ePROs are to be performed at Cycle 1, Cycle 2, Cycle 3, Cycle 4, Cycle 5 and every 2 cycles thereafter (eg, Cycle 7, Cycle 9) up to a year or End of Treatment, whichever comes first, and the 30-day post-treatment discontinuation follow-up visit. If the subject does not complete the ePROs the MISS_MODE form must be completed to capture the reason the assessment was not performed.
j. Vital signs to include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at Visit 1 only.
k. Pembrolizumab should be administered on Day 1 of each 3-week cycle after all procedures/assessments have been completed. Pembrolizumab 200 mg fixed dose 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. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (ie, infusion time is 30 minutes: -5 min/+10 min). Study treatment is discontinued after completion of 35 administrations (approximately 2 years).
l. For women of reproductive potential, a serum pregnancy test should be performed within 72 hours prior to each cycle of trial treatment and 30 days post treatment. A urine test can be considered if serum is not appropriate. Pregnancy tests (serum and/or urine tests) should be repeated if required by local guidelines.
m. Coagulation factors (PT/INR and aPTT) should be tested as part of the screening procedures for all subjects. And to be performed within 10 days of the first dose of trial treatment.
n. ECOG PS for screening is to be performed within 3 days prior to the first dose of trial treatment. Laboratory tests for screening are to be performed within 10 days prior to the first dose of trial treatment. See Section 7.1.3 for details regarding laboratory tests. After Cycle 1, lab samples can be collected up to 72 hours prior to the scheduled time point. CBC with Differential, Chemistry panel, are to be repeated every 2 cycles after Cycle 6 (eg, Cycle 8-Day 1, Cycle 10-Day 1). Thyroid function tests should be collected every 6 weeks (every 2 cycles, eg, Cycles, 8, 10, 12, etc). Unresolved abnormal labs that are drug related AEs should be followed until resolution. Labs do not need to be repeated after the end of treatment if labs are within normal range.
o. Serum CEA and CA19-9 tests for screening are to be performed within 10 days prior to the first dose of trial treatment. See Section 7.1.3 for details regarding laboratory tests. After Cycle 1, lab samples can be collected up to 72 hours prior to the scheduled time point. Serum CEA and CA19-9 should be collected at screening (baseline), Cycle 3 and every 6 weeks (conducted at corresponding study visits; Cycle 5, Cycle 7, etc.) until study treatment discontinuation.

p. This sample should be drawn for planned genetic analysis of DNA and drug response unless there is either a documented law or regulation prohibiting collection, or unless the IRB/IEC does not approve of the collection of the sample for these purposes. If the sample is collected, any leftover extracted DNA will be stored for future biomedical research if the subject signs the FBR consent. Detailed instructions for the collection and management of specimens are provided in the Procedures Manual and Section 12.2.

q. Whole blood sample for correlative studies should be collected at Cycle 1, Day 1- Pre-dose, Cycle 2 Day 1- Pre-dose, Cycle 3 Day 1 Pre-dose and again at treatment discontinuation. Blood for serum and blood for plasma to be collected only prior to the first dose of trial treatment. See Procedures Manual.

r. Baseline tumour imaging will be performed within **21** days prior to randomization. Scans performed as part of routine clinical management are acceptable for use as the baseline scan if they are of diagnostic quality and performed within the allotted screening window for each cohort. The exact same image acquisition and processing parameters should be used throughout the study. The first on-study imaging time point will be performed 6 weeks (± 7 days) after the subject has been randomized, or earlier if clinically indicated and will continue to be performed every 6 weeks (± 7 days) until PD. Imaging timing should follow calendar days. All on-study scans (scheduled and unscheduled) should be submitted to the central imaging vendor.

s. In subjects who discontinue study therapy without centrally verified disease progression, a radiologic evaluation should be performed at the time of treatment discontinuation (ie, date of 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 required. These subjects should be assessed every 6 weeks (42 ± 7 days) by radiologic imaging to monitor disease status until the start of new anti-cancer therapy, disease progression determined by the central imaging vendor, death, or end of study.

t. Baseline tumour tissue for biomarker analysis from newly obtained core or excisional biopsy (FNA not adequate) and archival tissue sample (where available) should be tested for PD-L1. Only PD-L1 positive subjects will be eligible for this trial. Tumour submission can occur up to 28 days prior to randomization. Consent must be obtained prior to tumour tissue submission/collection. Detailed instructions for tissue collection, process and shipment are provided in the Procedures Manual. If the subject signs the Future Biomedical Research (FBR) consent, any leftover tissue that would ordinarily be discarded at the end of the main study will be retained for FBR. An optional newly-obtained core or excisional biopsy (FNA not adequate) can be collected at Discontinuation for PD. This biopsy is requested but not required. Endoscopic biopsies are permitted.

6.1.2 Treatment Arm 2 and 3: Pembrolizumab + Chemotherapy and Placebo + Chemotherapy

Trial Period:	Screening Phase		Treatment Cycles[a]						End of Treatment	Post-Treatment		
Treatment Cycle	Tumour Tissue collection/submission	Screening	1	2	3	4	5	Cycle 6 and beyond	Last Dose	Safety Follow-up	Follow Up Visits[b]	Survival Follow-up[c]
									At time of treatment discon	30 days post discontinuation	Every 6 weeks post discontinuation	Every 12 weeks
Scheduling Window (Days)[d]:	-28 to -1	-21 to -1		± 3	± 3	± 3	± 3	± 3	± 3	± 7	± 7	± 7
Administrative Procedures												
Informed Consent[e]	X											
Informed Consent for Future Biomedical Research[f]	X											
Inclusion/Exclusion Criteria		X										
Subject Identification Card		X										
Demographics and Medical History		X										
Prior and Concomitant Medication Review[g]		X	X	X	X	X	X	X	X	X		
Clinical Procedures/Assessments												
Review Adverse Events[h]	X	X	X	X	X	X	X	X	X	X	X	
ePROs (HRQoL Measures)[i]			X	X	X	X	X[i]		X	X		
12-Lead ECG (Local)		X										
Full Physical Examination[w]		X							X			
Directed Physical Examination[w]			X	X	X	X	X	X				
Vital Signs and Weight[j]		X	X	X	X	X	X	X	X			
ECOG Performance Status[p]		X	X	X	X	X	X	X	X			
Post-study Anticancer Therapy Status											X	X
Survival Status[x]			←	—	—	—	—	—	—	—	—	X →
Trial Treatment Administration												
Pembrolizumab/Placebo[k]			X	X	X	X	X	X				
Cisplatin[l]			X	X	X	X	X	X				
5-FU or Capecitabine[m]			X	X	X	X	X	X				
Laboratory Procedures/Assessments: Analysis performed by LOCAL Laboratory												
Pregnancy Test – Serum or Urine[n]		X		X	X	X	X	X		X		
PT/INR and aPTT[o]		X										
CBC with Differential[p]		X		X	X	X	X	X	X	X		

Trial Period:	Screening Phase		Treatment Cycles[a]						End of Treatment	Post-Treatment		
Treatment Cycle	Tumour Tissue collection/submission	Screening	1	2	3	4	5	Cycle 6 and beyond	Last Dose	Safety Follow-up	Follow Up Visits[b]	Survival Follow-up[c]
									At time of treatment discon	30 days post discontinuation	Every 6 weeks post discontinuation	Every 12 weeks
Scheduling Window (Days)[d]:	-28 to -1	-21 to -1		± 3	± 3	± 3	± 3	± 3	± 3	± 7	± 7	± 7
Chemistry Panel[p]		X		X	X	X	X	X	X	X		
Urinalysis[p]		X										
T3 (or Free T3), FT4 and TSH[p]		X		X		X		X		X		
Serum carcinoembryonic antigen (CEA)[q]		X			X		X	X[q]				
Serum CA19-9[q]		X			X		X	X[q]				
Laboratory Procedures/Assessments: Analysis performed by CENTRAL laboratory												
Blood for Genetics[r]			X									
Correlative Blood Samples (DNA)[s]			X	X	X				X			
Correlative Blood Samples (RNA)[s]			X	X	X				X			
Correlative Blood Samples (plasma)[s]			X									
Correlative Blood Samples (serum)[s]			X									
Efficacy Measurements												
Tumour Imaging[t]		X			X		X	X[t]	X[u]		X[u]	
Tumour Tissue Collection												
Archival or Newly Obtained Tissue Collection[v]	X								X			

a. Unless otherwise specified, assessments/procedures are to be performed on Day 1 and prior to the first dose of treatment for each cycle unless otherwise specified.
b. In subjects who discontinue study therapy without documented disease progression, every effort should be made to continue monitoring their disease status by radiologic imaging every 6 weeks (± 7 days) until (1) the start of new anti-cancer treatment, (2) disease progression as assessed by the central imaging vendor, (3) death, or (4) the end of the study, whichever occurs first.
c. After the start of new anti-cancer treatment or documented disease progression by the central imaging vendor, the subject should be contacted by telephone every 12 weeks to assess for survival status. Note: Every effort should be made to ensure telephone contact at least 90 days post discontinuation to capture SAEs/ECIs The Sponsor may request survival status be assessed at additional time points during the course of the study. For example, these additional time points may be requested prior to; an eDMC safety review, efficacy interim analysis, and/or final analysis. All subjects who are not known to have died prior to the request for these additional survival status time points will be contacted at that time.
d. Unless otherwise specified, the window for each visit is ± 3 days. Cycle 1 treatment must be given within 3 days of randomization.
e. Written consent must be obtained prior to performing any protocol specified 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 (eg, within 21 days prior to the first dose of trial treatment). Screening number will be assigned when the study informed consent is signed.
f. Signing the informed consent for future biomedical research (FBR) sample is optional. Detailed instructions for the collection and management of specimens for FBR are provided in the Procedures Manual and Section 12.2.
g. Prior medications – Record all medications taken within 30 days of first dose. Concomitant medications – Enter new medications started during the trial through the Safety Follow-up visit. Record all medications taken for SAEs as defined in Section 7.2.
h. Record all AEs occurring within 30 days after the last dose of trial treatment. Report all SAEs (related and unrelated to trial treatment) and ECIs occurring up until 90 days after the last dose of trial treatment or 30 days after the end of treatment if the subject initiates new anticancer therapy, whichever occurs first. Afterwards, report only SAEs and ECIs that are related to trial treatment.
i. It is strongly recommended that electronic patient reported outcomes (ePROs) are administered prior to drug administration, adverse event evaluation and disease status notification starting with the EQ5D-3L, followed by EORTC QLQ-C30, and EORTC QLQ-ST022; an exception to this recommendation may occur at the treatment discontinuation visit where subjects may have already been notified of their disease status or an AE evaluation is known prior to them arriving to the clinic. All ePROs All ePROs are to be performed at Cycle 1, Cycle 2, Cycle 3, Cycle 4, Cycle 5 and every 2 cycles thereafter (eg, Cycle 7, Cycle 9) up to a year or End of Treatment, whichever comes first, and the 30-day post-treatment discontinuation follow-up visit. If the subject does not complete the ePROs the MISS_MODE form must be completed to capture the reason the assessment was not performed.
j. Vital signs to include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at Visit 1 only.
k. Pembrolizumab should be administered on Day 1 of each 3-week cycle after all procedures/assessments have been completed. Pembrolizumab 200 mg 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. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (ie, infusion time is 30 minutes: -5 min/+10 min). For subjects randomized to the pembrolizumab/placebo plus cisplatin +5-FU arm, the pembrolizumab/placebo infusion is administered first followed by the cisplatin infusion and then 5-FU infusion.
l. 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.
m. 5-FU 800 mg/m^2/day will be administered as a continuous IV infusion from Day 1 to Day 5 (120 hours) of each treatment cycle. Although use of 5-FU infusion is preferred, Capecitabine1000 mg/m2 bid Day 1 to Day 14 Q3W may be permitted according to local guideline at Investigator decision. Decision regarding the type of comparator used (5-FU or capecitabine) should be determined prior to randomization in the trial.
n. For women of reproductive potential, a serum pregnancy test should be performed within 72 hours prior to each cycle of trial treatment and 30 days post treatment. A urine test can be considered if serum is not appropriate. Pregnancy tests (serum and/or urine tests) should be repeated if required by local guidelines.
o. Coagulation factors (PT/INR and aPTT) should be tested as part of the screening procedures for all subjects. And to be performed within 10 days prior to the first dose of trial treatment.
p. ECOG PS for screening is to be performed within 3 days prior to the first dose of trial treatment. Laboratory tests for screening are to be performed within 10 days prior to the first dose of trial treatment. See Section 7.1.3 for details regarding laboratory tests. After Cycle 1, lab samples can be collected up to 72 hours prior to the scheduled time point. CBC with Differential, Chemistry panel, are to be repeated every 2 cycles after Cycle 6 (eg, Cycle 8-Day 1, Cycle 10-Day 1). Thyroid function

tests should be collected every 6 weeks (every 2 cycles, eg, Cycles, 8, 10, 12, etc). Unresolved abnormal labs that are drug related AEs should be followed until resolution. Labs do not need to be repeated after the end of treatment if labs are within normal range.

q. Serum CEA and CA 19-9 should be collected at screening (baseline), Cycle 3 and every 6 weeks (conducted at corresponding study visit; Cycle 5, Cycle 7, etc.) until study treatment discontinuation.

r. This sample should be drawn for planned genetic analysis of DNA and drug response unless there is either a documented law or regulation prohibiting collection, or unless the IRB/IEC does not approve of the collection of the sample for these purposes. If the sample is collected, any leftover extracted DNA will be stored for future biomedical research if the subject signs the FBR consented. Detailed instructions for the collection and management of specimens are provided in the Procedures Manual and Section 12.2

s. Whole blood sample for correlative studies should be collected at Cycle 1, Day 1- Pre-dose, Cycle 2 Day 1- Pre-dose, Cycle 3 Day 1 Pre-dose and again at treatment discontinuation. Blood for serum and blood for plasma to be collected only prior to the first dose of trial treatment. See Procedures Manual.

t. Baseline tumour imaging will be performed within **21** days prior to randomization. Scans performed as part of routine clinical management are acceptable for use as the baseline scan if they are of diagnostic quality and performed within the allotted screening window for each cohort. The exact same image acquisition and processing parameters should be used throughout the study. The first on-study imaging time point will be performed 6 weeks (± 7 days) after the subject has been randomized, or earlier if clinically indicated and will continue to be performed every 6 weeks (± 7 days) until PD. Imaging timing should follow calendar days. On-study scans (scheduled and unscheduled) should be submitted to the central imaging vendor.

u. In subjects who discontinue study therapy without centrally verification of disease progression, a radiologic evaluation should be performed at the time of treatment discontinuation (ie, date of 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 required. These subjects should be assessed every 6 weeks (42 ± 7 days) by radiologic imaging to monitor disease status until the start of new anti-cancer therapy, disease progression determined by the central imaging vendor, death, or end of study.

v. Baseline tumour tissue for biomarker analysis from newly obtained core or excisional biopsy (FNA not adequate) and archival tissue sample (where available) should be tested for PD-L1. Only PD-L1 positive subjects will be eligible for this trial. Tumour submission can occur up to 28 days prior to randomization. Consent must be obtained prior to tumour tissue submission/collection. Detailed instructions for tissue collection, process and shipment are provided in the Procedures Manual. If the subject signs the Future Biomedical Research (FBR) consent, any leftover tissue that would ordinarily be discarded at the end of the main study will be retained for FBR. An optional newly obtained core or excisional biopsy (FNA not adequate) can be collected at Discontinuation for PD. This biopsy is requested but not required. Endoscopic biopsies are permitted

w. Full physical exam and directed physical exam will include neurologic exam to be performed by the treating physician or designee. Audiometry testing will be performed at baseline, and is repeated during the study as clinically indicated per the treating physician or designee.

x. After documented local site assessed disease progression, or the start of new anticancer treatment; contacts are approximately every 12 weeks by telephone. 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).

6.2 Second Course Phase (Retreatment with Pembrolizumab)

Trial Period:	Treatment Cycles[a]						End of Treatment	Post-Treatment		
Treatment Cycle:	1	2	3	4	5	Cycle 6 and beyond	Last Dose	Safety Follow-up	Follow Up Visits[b]	Survival Follow-up[c]
							At time of treatment discon	30 days post discontinuation	Every 6 weeks post discontinuation	Every 12 weeks
Scheduling Window (Days)[d]:	-3	± 3	± 3	± 3	± 3	± 3	± 3	± 7	± 7	± 7
Administrative Procedures										
Eligibility Criteria[e]	X									
Concomitant Medication Review[f]	X	X	X	X	X	X	X	X		
Clinical Procedures/Assessments										
Review Adverse Events[g]	X	X	X	X	X	X	X	X	X	
Full Physical Examination	X						X			
Directed Physical Examination		X	X	X	X	X				
Vital Signs and Weight[h]	X	X	X	X	X	X	X	X		
ECOG Performance Status[k]	X	X	X	X	X	X	X			
Pembrolizumab Administration	X	X	X	X	X	X				
Post-study Anticancer Therapy Status									X	X
Survival Status[n]	←	—	—	—	—	—	—	—	→	X
Laboratory Procedures/Assessments: Analysis performed by LOCAL laboratory										
Pregnancy Test – Urine or Serum[i]	X	X	X	X	X	X		X		
PT/INR and aPTT[j]	X									
CBC with Differential[k]	X	X	X	X	X	X[k]	X	X		
Chemistry Panel[k]	X	X	X	X	X	X[k]	X	X		
Urinalysis[k]	X									
T3(or Free T3), FT4 and TSH[k]	X		X		X			X		
Efficacy Measurements										
Tumour Imaging[l]	X		X		X	X	X[m]		X[m]	

a. In general, assessments/procedures are to be performed on Day 1 and prior to the first dose of treatment for each cycle unless otherwise specified. Treatment cycles are 3 weeks.
b. In subjects who discontinue study therapy without documented disease progression, every effort should be made to continue monitoring their disease status by radiologic imaging every 6 weeks (42 ± 7 days) up to week 30 or every 9 weeks (± 7 days) if after Week 30, until (1) the start of new anti-cancer treatment, (2) disease progression as assessed by the central imaging vendor, (3) death, or (4) the end of the study, whichever occurs first.
c. After the start of new anti-cancer treatment or documented disease progression by the central imaging vendor, the subject should be contacted by telephone every 12

weeks to assess for survival status. The Sponsor may request survival status be assessed at additional time points during the course of the study. For example, these additional time points may be requested prior to; an eDMC safety review, efficacy interim analysis, and/or final analysis. All subjects who are not known to have died prior to the request for these additional survival status time points will be contacted at that time.

d. In general, the window for each visit is ± 3 days unless otherwise noted.
e. Subjects who either a) attain a CR and discontinue treatment or b) discontinue treatment after 35 administrations (approximately 2 years) on study treatment for reasons other than disease progression or intolerability may restart trial treatment if they meet the criteria specified in Section 7.1.5.2.1.
f. Concomitant medications – Enter new medications started during the trial through the Safety Follow-up visit. Record all medications taken for SAEs as defined in Section 7.2.
g. Record all AEs occurring within 30 days after the last dose of trial treatment. Report all SAEs (related and unrelated to trial treatment) and ECIs occurring up until 90 days after the last dose of trial treatment or 30 days after the end of treatment if the subject initiates new anticancer therapy, whichever occurs first. Afterwards, report only SAEs and ECIs that are related to trial treatment.
h. Vital signs to include temperature, pulse, respiratory rate, weight and blood pressure.
i. For women of reproductive potential, a serum pregnancy test should be performed within 72 hours prior to each cycle of trial treatment and 30 days post treatment. A urine test can be considered if serum is not appropriate. Pregnancy tests (serum and/or urine tests) should be repeated if required by local guidelines.
j. Coagulation factors (PT/INR and aPTT) should be tested as part of the screening procedures for all subjects. And may be performed within 10 days prior to the first retreatment dose of pembrolizumab.
k. ECOG PS for screening is to be performed within 3 days prior to the first dose of trial treatment. Laboratory tests for screening are to be performed within 10 days prior to the first dose of trial treatment. See Section 7.1.3 for details regarding laboratory tests. After Cycle 1, lab samples can be collected up to 72 hours prior to the scheduled time point. See Section 7.1.3 for details regarding laboratory tests. To be repeated every 2 cycles after Cycle 5. CBC with Differential, Chemistry panel, are to be repeated every 2 cycles after Cycle 6 (eg, Cycle 8-Day 1, Cycle 10-Day 1). Thyroid function tests should be collected every 6 weeks (every 2 cycles, eg, Cycles, 7, 9, 11, etc). Unresolved labs that are drug related AEs should be followed until resolution. Labs do not need to be repeated after the end of trial treatment if labs are within normal range.
l. A scan must be performed within 21 days prior to restarting treatment with pembrolizumab. Imaging should continue to be performed every 6 weeks (42 ± 7 days) after the first dose of trial retreatment or more frequently if clinically indicated. Imaging timing should follow calendar days and should not be adjusted for any dose modifications. The exact same image acquisition and processing parameters should be used throughout the study.
m. In subjects who discontinue study therapy without confirmed disease progression, a radiologic evaluation should be performed at the time of treatment discontinuation (ie, date of 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 isn't mandatory
n. After documented local site assessed disease progression, or the start of new anticancer treatment; contacts are approximately every 12 weeks by telephone.

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).

7.0 TRIAL PROCEDURES

7.1 Trial Procedures

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

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

7.1.1 Administrative Procedures

7.1.1.1 Informed Consent

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

7.1.1.1.1 General Informed Consent

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

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

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

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

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

7.1.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

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

7.1.1.2 Inclusion/Exclusion Criteria

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

7.1.1.2.1 Submitting Tumour Sample

Per inclusion 7 in Section 5.1.2, tumour tissue sample for assessment of PD-L1 status must meet the following requirement:

Either pre-existing archived or newly-obtained (fresh tissue) biopsy specimens from either primary or metastatic tumour of gastric origin, whichever most recent.

- Newly-obtained (fresh tissue) is defined as a specimen obtained up to 42 days prior to administration of study treatment on Day 1 of Cycle 1, and no additional anti-cancer treatment has been given after the specimen was obtained.

- Pre-existing, archived tissue must be obtained prior to time point that any anti-cancer treatment was given.

A fine needle aspirate (FNA) or cytologic specimen will not be acceptable. In the event the most recent available tumour tissue specimen is an FNA or cytologic specimen, a previous specimen obtained prior to any anti-cancer therapy was given may be submitted (provided it is not an FNA or cytologic specimen).

Where available, both newly-obtained (fresh tissue) and pre-existing archived tissues are requested; however, the tissue specimen obtained closest to study treatment initiation on Day 1 of Cycle 1 will be used to determine eligibility for study participation while the older tissue specimen will be used for subsequent analysis to compare performance of PD-L1 assessment in newly-obtained (fresh tissue) vs. archived tissue samples.

Tumour tissue specimen submitted in either formalin solution or FFPE block is acceptable. If submitting unstained cut slides from FFPE block, freshly cut slides should be received by the central laboratory within 14 days from when the slides are prepared. Please refer to the Procedures Manual for additional details.

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.

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

7.1.1.4 Medical History

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

7.1.1.5 Disease Details

The investigator or qualified designee will obtain prior and current details regarding the subject's gastric or GEJ adenocarcinoma.

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 disease for which the subject has enrolled in this trial 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 from the time of signing the informed consent through the Safety Follow-up visit. In addition, new medications started during the Second Course Phase through the Second Course Safety Follow-up visit should be recorded.

All medications related to reportable SAEs and ECIs should be recorded as defined in Section 7.2.

7.1.1.7 Assignment of Screening Number

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

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

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

7.1.1.8 Assignment of Randomization Number

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

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

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

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

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

Administration of trial medication will be witnessed by the investigator and/or trial staff while the subject is in the treatment centre.

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

For those medications taken at home, subjects will be provided a medication diary in which they will record trial medication doses and will be instructed to bring this diary and trial medication containers with them when they at the time of clinic visits.

7.1.2 Clinical Procedures/Assessments

7.1.2.1 Adverse Event (AE) Monitoring

The investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs as specified in the TRIAL FLOW CHART and more frequently if clinically indicated. Adverse events will be graded and recorded throughout the trial and during the follow-up period according to NCI CTCAE Version 4.0 (see Section 12.6). Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

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

7.1.2.2 Physical 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 timepoints for full physical exams are described in Section 6. After the first dose of trial treatment new clinically significant abnormal findings should be recorded as AEs.

7.1.2.2.2 Directed Physical Exam

For cycles that do not require a full physical exam as defined in Section 6, the investigator or qualified designee will perform a directed physical exam as clinically indicated prior to the administration of the trial treatment. New clinically significant abnormal findings should be recorded as AEs.

7.1.2.3 Vital Signs

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

7.1.2.4 12-Lead Electrocardiogram (ECG)

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

7.1.2.5 Eastern Cooperative Oncology Group (ECOG) Performance Status

The investigator or qualified designee will assess ECOG status (see Section 12.5) at screening, prior to dosing on Day 1 of each treatment cycle and at discontinuation of trial treatment as specified in the Trial Flow Chart.

7.1.2.6 Tumour 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 (SIM).

Tumour imaging is strongly preferred to be acquired by computed tomography (CT). Magnetic resonance imaging (MRI) 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 tumour burden.

7.1.2.6.1 Initial Tumour Imaging

Initial tumour 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 prior to submitting to central imaging vendor.

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 tumour 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.

Subjects with previously treated brain metastases may participate provided they have stable brain metastases, ie, without evidence of progression by imaging (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 as per local site assessment. This exception does not include carcinomatous meningitis, as subjects with carcinomatous meningitis are excluded regardless of clinical stability.

7.1.2.6.2 Tumour Imaging During Trial

The first on-study imaging assessment should be performed at 6 weeks (42 days ± 7 days) after the subject has been randomized. Subsequent imaging should be performed every 6 weeks (42 days ± 7 days) or more frequently if clinically indicated. After 1 year, subjects who remain on treatment will have imaging performed every 6 weeks (42 ± 7 days). Imaging timing should follow calendar days and should not be adjusted for delays in cycle starts. Imaging should continue to be performed until disease progression verified by the central imaging vendor (unless the site Principal Investigator [PI] elects to continue treatment and follow irRECIST), the start of new anticancer treatment, withdrawal of consent, or death. All supplemental imaging must be submitted to the central imaging vendor.

Per RECIST 1.1, PR and CR should be confirmed by a repeat tumour imaging assessment obtained 4 weeks or longer from the date the response was first documented. of the tumour 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 (ie. 6 weeks later), whichever is clinically indicated.

Subjects will then report to regularly scheduled imaging, starting with the next scheduled imaging time point. Subjects who obtain a confirmation scan do not need to undergo the next scheduled tumour imaging if it is <4 weeks later; tumour imaging may resume at the subsequent scheduled imaging time point. Per irRECIST (Section 7.1.2.6.6 Immune-related RECIST (irRECIST)), disease progression on subjects treated with pembrolizumab 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 disease progression may continue on treatment at the discretion of the site Investigator until progression is confirmed by the site provided they have met the conditions detailed in Section 7.1.2.6.6. Subjects who obtain a confirmation scan do not need to undergo the next scheduled tumour imaging if it is <4 weeks later; tumour imaging may resume at the subsequent scheduled imaging time point if clinically stable. Subjects who have confirmed disease progression, as assessed by the site, will discontinue trial treatment. Exceptions are detailed in Section 7.1.2.6.6.

7.1.2.6.3 End of Treatment and Follow-up Tumour Imaging

In subjects who discontinue trial treatment, tumour 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 disease progression, this is the final required tumour imaging. In subjects who discontinue trial treatment without documented disease progression, every effort should be made to continue monitoring their disease status by tumour imaging using the same imaging schedule used while on treatment to monitor disease status until the start of a new anticancer treatment, disease progression, death, or the end of the trial, whichever occurs first.

7.1.2.6.4 Second Course (Retreatment) Tumour Imaging

A scan must be performed within 21 days prior to restarting treatment with pembrolizumab. Local reading (investigator assessment with site radiology reading) will be used to determine eligibility. Imaging should be submitted to the central imaging vendor for retrospective review. The first on-trial imaging assessment should be performed at 6 weeks (42 ±7 days) after the restart of treatment. Subsequent tumour imaging should be performed every 6 weeks (42 ±7 days) or more frequently if clinically indicated. If tumour imaging shows initial PD per RECIST 1.1, tumour assessment should be repeated ≥4 weeks later in order to confirm PD with the option of continuing treatment while awaiting radiologic confirmation of progression. Subjects who obtain a confirmation scan do not need to undergo scheduled tumour imaging if it is <4 weeks later and may wait until the next scheduled imaging time point if clinically stable. Imaging should continue to be performed until disease progression, the start of a new anticancer treatment, withdrawal of consent, death, or notification by the Sponsor, whichever occurs first. Disease progression may be confirmed at least 4 weeks after the first tumour imaging indicating PD in clinically stable subjects. Additional irRECIST detail is described in Section 7.1.2.6.6.

In subjects who discontinue trial treatment, tumour 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 disease progression, this is the final required tumour imaging.

In subjects who discontinue trial treatment without documented disease progression, every effort should be made to continue monitoring their disease status by radiologic imaging every 6 weeks (42 ±7 days) until either the start of a new anticancer treatment, disease progression, death, or the end of the trial, whichever occurs first.

Subjects on the placebo+cisplatin+ 5-FU arm are not eligible for this course of therapy.

7.1.2.6.5 RECIST 1.1

RECIST 1.1 will be used by BICR as the primary measure for assessment of tumour response, date of disease progression, and as a basis for all protocol guidelines related to disease status (eg, discontinuation of trial therapy). Although RECIST 1.1 references a maximum of 5 target lesions in total and 2 per organ, the Sponsor allows a maximum of 10 lesions in total and 5 per organ, if clinically relevant to enable a broader sampling of tumour burden.

Initial tumour imaging showing site-assessed PD should be submitted to the central imaging vendor immediately for verification of PD by BICR. The site will be notified if the BICR verifies PD using RECIST 1.1. The first half of the flow chart in Figure 1 illustrates the imaging flow involving verification of PD for clinically stable subjects.

7.1.2.6.6 Immune-related RECIST (irRECIST)

irRECIST is RECIST 1.1 adapted as described below to account for the unique tumour response seen with immunotherapeutic drugs. irRECIST will be used by the site Investigator/local radiology reviewers to assess tumour response and progression, and make treatment decisions. This data will be collected in the clinical database. When feasible, subjects treated with pembrolizumab 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 tumour 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 tumour imaging for confirmation of PD. Tumour 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 treated with pembrolizumab 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 PI whether to continue a subject on trial medication until repeat imaging is obtained (using irRECIST for subject management. 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 tumour

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 tumour 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 tumour 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 (ie, 2 scans at least 4 weeks apart demonstrating PD) per irRECIST, but the subject is achieving a clinically meaningful benefit, and there is no further increase in the tumour burden at the confirmatory tumour imaging, an exception to continue treatment may be considered following consultation with the Sponsor. In this case, if treatment is continued, tumour imaging should continue to be performed following the intervals as outlined in Section 6.0 and be submitted to the central imaging vendor.

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

7.1.2.7 Electronic Patient Reported Outcomes (ePROs)

The EuroQol EQ5D-3L, EORTC QLQ-C30, and EORTC QLQ-STO22 questionnaires will be administered by trained study site personnel and completed electronically by subjects. It is strongly recommended that the electronic EORTC QLQ-C30, EORTC QLQ-STO22 and EuroQol EQ5D-3L are completed by the subject prior to drug administration, AE evaluation and disease status notification; an exception to this recommendation may occur at the treatment discontinuation visit. ePROs will be administrated in the following order: EuroQol EQ5D-3L first, then EORTC QLQ-C30, and lastly the EORTC QLQ-STO22 at the time points specified in the Trial Flow Chart.

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 Procedure Trial Procedures Manual. Refer to the TRIAL FLOW CHART (Section 6) 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 10.

Table 10 Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Blood	Serum β-human chorionic gonadotropin (β-hCG)[c]
Hemoglobin	Alkaline phosphatase	Glucose	PT (INR)
Platelet count	Alanine aminotransferase (ALT)	Protein	aPTT
WBC (total and differential)[a]	Aspartate aminotransferase (AST)	Specific gravity	Total triiodothyronine (T3) or Free T3
Absolute Neutrophil Count	Carbon dioxide (CO_2 or bicarbonate)[b]	Microscopic exam, if abnormal results are noted	Free thyroxine (T4)
Absolute Lymphocyte Count	Calcium	Urine pregnancy test[c]	Thyroid stimulating hormone (TSH)
	Chloride		
	Creatinine		
	Glucose		
	Magnesium		
	Phosphorus		
	Potassium		
	Sodium		
	Total Bilirubin		
	Direct Bilirubin, if total bilirubin is elevated above the upper limit of normal		
	Total protein		
	Blood Urea Nitrogen/Urea[d]		
	Uric acid		

a. Absolute or % is acceptable.
b. If these tests are not done as part of standard of care in your region then these tests do not need to be performed.
c. Perform on women of childbearing potential only. Serum pregnancy test is preferred but urine test can be considered if serum not appropriate.
d. Blood Urea Nitrogen is preferred; if not available urea may be tested.

Laboratory tests for screening should be performed within 10 days prior to the first dose of trial treatment. An exception is hepatitis and thyroid serologies, which may be performed within 28 days prior to first dose. Subjects eligible for trial retreatment should have imaging performed within 21 days and laboratory tests performed within 7 days prior to the first dose

of trial treatment in the Second Course Phase. After Cycle 1, in both the Initial Treatment Phase and the Second Course Phase, pre-dose laboratory safety tests can be conducted up to 72 hours prior to dosing unless otherwise noted on the flow charts.

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.

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

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 each cycle of trial treatment and 30 days post-treatment. 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 Pharmacokinetic/Pharmacodynamic Evaluations

7.1.3.3.1 Blood Collections – Samples for Correlative and Genetic Analyses

Details regarding time points for blood collection are outlined in the Trial Flow Chart – Section 6.1.

Samples for planned, exploratory genetic analysis of DNA should be drawn unless there is a documented law or regulation prohibiting collection, or unless the IRB/IEC does not approve of the collection.

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

Any leftover specimens may be used for future biomedical research provided the subject has provided the relevant informed consent.

7.1.3.4 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/tumour DNA and drug response. If a documented law or regulation prohibits (or local IRB/Independent Ethics Committee [IEC] 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 Future Biomedical Research consent.

7.1.3.5 Future Biomedical Research

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

- Leftover DNA
- Leftover archival tumour tissue or leftover newly obtained biopsy samples taken throughout the trial

7.1.4 Other Procedures

7.1.4.1 Withdrawal/Discontinuation

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

When a subject discontinues/withdraws from participation in the trial, all applicable activities scheduled for the end of treatment visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.2 - Assessing and Recording Adverse Events. Subjects on the pembrolizumab arms who a) attain a CR or b) complete 35 administrations (approximately 2 years) of study treatment may discontinue treatment with the option of restarting treatment if they meet the criteria specified in Section 7.1.2.6.4. 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 7.1.5.3.1) and then proceed to the Follow-up Period of the study (described in Section 7.1.5.3.2).

7.1.4.1.1 Withdrawal From Future Biomedical Research

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

In the event that the medical records for the main trial are no longer available (e.g., if the investigator is no longer required by regulatory authorities to retain the main trial records) or the specimens have been completely anonymized, there will no longer be a link between the

subject's personal information and their specimens. In this situation, the request for specimen destruction cannot be processed.

7.1.4.1.2 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 counselled 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 Blinding/Unblinding

IVRS/IWRS should be used for emergency unblinding in the event that this is required for subject safety.

The study is partially blinded, refer to Section 5.2.3.

Even though the trial is only partially blinded (ie treatment arm 1 is open label), the following measures will be taken to help maintain internal blinding: imaging data are centrally reviewed, and the central reviewer is blinded to subject treatment assignment.

The emergency unblinding call centre will use the randomization schedule for the trial to unblind subjects and to unblind treatment identity for subjects enrolled in treatment group 2 or 3 of this trial. In the event that the emergency unblinding call centre is not available for a given site in this trial, the central electronic randomization system (IVRS/IWRS) should be used in order to unblind subjects and to unblind treatment identity. The Sponsor will not provide random code/disclosure envelopes or lists with the clinical supplies.

Treatment identification information is to be unblinded ONLY in following situation:

1. For the welfare of the subject, if necessary.

2. Subjects requiring second course/re-retreatment who achieved SD or better during first course of treatment and has to discontinue for reason other than disease progression or intolerability. Such subject must have experienced radiographic

disease progression while off study treatment according to the criteria in Section 7.1.5.2.1.

Every effort should be made to avoid unblinding the subject unless necessary. In the event that unblinding has occurred, the circumstances around the unblinding (eg, date and reason) must be documented promptly, and the Sponsor Clinical Director notified as soon as possible. Only the principal investigator or delegate and the respective subject's code should be unblinded.

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 study 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 study site.

7.1.5 Visit Requirements

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

7.1.5.1 Screening

Within 21 days prior to treatment randomization, potential subjects will be evaluated to determine that they fulfil the entry requirements as set forth in Section 5.1. Visit requirements are outlined in the TRIAL FLOW CHART (Section 6). 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 21 days prior to the first dose of trial treatment except for the following:

ECOG PS for screening is to be performed within 3 days prior to the first dose of trial treatment. Laboratory tests for screening are to be performed within 10 days prior to the first dose of trial treatment. For women of reproductive potential, a serum pregnancy test will be performed within 72 hours prior to the first dose of trial treatment. A urine test may be considered if a serum test is not appropriate.

Subjects may be rescreened after initially failing to meet the inclusion/exclusion criteria. Results from assessments performed during the initial screening period are acceptable in lieu of a repeat screening test if performed within the specified time frame and the inclusion/exclusion criteria is met. Subjects who are rescreened will retain their original screening number.

7.1.5.2 Treatment Period

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

7.1.5.3 Post-Treatment Visits

7.1.5.3.1 Safety Follow-up Visit

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

Subjects who are eligible for retreatment/crossover with pembrolizumab may have up to 2 safety follow-up visits, 1 after the Initial Treatment Period and 1 after the Second Course Treatment.

7.1.5.3.2 Follow-up Visits

Subjects who discontinue trial treatment for a reason other than disease progression will move into the Follow-Up Phase and should be assessed 6 weeks (42 ± 7 days) to monitor disease status. The Sponsor may request survival status to be assessed at additional time points during the course of the study (not to exceed approximately 12 weeks). Every effort should be made to collect information regarding disease status until the start of new anticancer therapy, disease progression, death, end of trial (or if the subject begins retreatment with pembrolizumab as detailed in Section 7.1.2.6.4). Information regarding post-trial anticancer treatment will be collected if new treatment is initiated.

Subjects who are eligible to receive retreatment with pembrolizumab according to the criteria in Section 5.2.2 will move from the Follow-Up Phase to the Second Course Phase when they experience disease progression. Details are provided in Trial Flow Chart (Section 6) for retreatment with pembrolizumab.

7.1.5.3.3 Survival Follow-up

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

7.1.5.4 Survival Status

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

during the Sponsor defined time period will be contacted for their survival status (excluding subjects 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 randomization/treatment allocation 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 randomization/treatment allocation 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 EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

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

For purposes of this trial, an overdose will be defined as any dose exceeding the prescribed dose for the standard treatments by ≥20% and as ≥1000 mg (5 times the dose) of pembrolizumab. 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 randomization/treatment allocation 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 randomization/treatment allocation through 120 days following cessation of Sponsor's product, or 30 days following cessation of 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 cancer;
- Is associated with an overdose.

Refer to Table 11 for additional details regarding each of the above criteria.

For the time period beginning when the consent form is signed until randomization/treatment allocation, 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 randomization/treatment allocation through 90 days following cessation of treatment, or 30 days following cessation of 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 randomization/treatment allocation, 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 randomization/treatment allocation through 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, 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 to the Sponsor.

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

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

7.2.4 Evaluating Adverse Events

An investigator who is a qualified physician will evaluate all adverse events according to the NCI Common Terminology for Adverse Events (CTCAE), version 4.0. 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 experience to the single agent.

Table 11 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 cancer (although not serious per ICH definition, is reportable to the Sponsor within 24 hours to meet certain local requirements); **or**	
	Is associated with 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 external Data Monitoring Committee (eDMC) 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 a separate charter that is reviewed and approved by the DMC. The DMC will monitor the trial at an appropriate frequency, as described in the detailed DMC charter. The DMC will also make recommendations to the EOC regarding steps to ensure both subject safety and the continued ethical integrity of the trial.

8.0 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the trial. If, after the trial has begun, but prior to any unblinding, 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 E-9). Changes to exploratory or other non-confirmatory analyses made after the protocol has been finalized, but prior to unblinding, will be documented in a supplemental SAP (sSAP) and referenced in the Clinical Study Report (CSR) for the trial. Post hoc exploratory analyses will be clearly identified in the CSR.

8.1 Statistical Analysis Plan Summary

Key elements of the statistical analysis plan are summarized below; the comprehensive plan is provided in Sections 8.2-8.12.

<table>
<tr><td>Study Design Overview</td><td>A Randomized, Active-Controlled, Partially Blinded, Biomarker Select, Phase III Clinical Trial of Pembrolizumab as Monotherapy and in Combination with Cisplatin+5-Flourouracil (5-FU) versus Placebo+Cisplatin+5-FU, as first-line treatment in Subjects with Advanced Gastric or Gastroesophageal Junction (GEJ) Adenocarcinoma</td></tr>
<tr><td>Treatment Assignment</td><td>Approximately 750 subjects with advanced gastric or GEJ adenocarcinoma will be randomized in a 1:1:1 ratio among three treatment arms in this trial, stratified by geographic region, backbone therapy (5-FU vs capecitabine) and disease status (See Section 5.4 Stratification for details). The three treatment arms are as follows:
<table>
<tr><th>Treatment Arm</th><th>Treatment Dose and Schedule</th></tr>
<tr><td>Treatment Arm 1</td><td>Pembrolizumab 200 mg every 3 weeks (Q3W)</td></tr>
<tr><td>Treatment Arm 2*</td><td>Pembrolizumab 200 mg + 5-FU 800 mg/m^2/day continuous IV infusion Days 1-5 + Cisplatin 80 mg/m^2 administrated Q3W</td></tr>
<tr><td>Treatment Arm 3*</td><td>Placebo+5-FU 800 mg/m^2/day continuous IV infusion Days 1-5 + Cisplatin 80 mg/m^2 administrated Q3W</td></tr>
<tr><td colspan="2">Although use of 5-FU infusion is preferred, Capecitabine 1000 mg/m^2 bid Day 1 to Day 14 Q3W may be permitted according to local guideline at Investigator’s discretion. Investigator decision regarding the type of comparator used should be determined prior to randomization in the trial.
*This is a partially blinded trial. Treatment Arm 1 is open label and Treatment Arm 2 and 3 are blinded.</td></tr>
</table></td></tr>
<tr><td>Analysis Populations</td><td>Efficacy: Intention-to-treat (ITT) population.
Safety: All Subjects as Treated (ASaT)</td></tr>
</table>

Primary Endpoint	1. Progression-free survival (PFS) – per RECIST 1.1 by blinded central radiologists' review 2. Overall Survival (OS)
Statistical Methods for Key Efficacy Analyses	The primary hypothesis for OS (H2 and H3) and PFS (H1) will be evaluated by comparing pembrolizumab in combination with SOC (cisplatin+5-FU or Capecitabine) versus SOC (cisplatin+5-FU or Capecitabine) using a stratified log-rank test. Estimation of the hazard ratio 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. The primary hypothesis for non-inferiority (H4) of pembrolizumab monotherapy vs. SOC for OS will be evaluated using a stratified Cox regression model. The OS primary hypothesis for superiority (H5 and H6) of pembrolizumab monotherapy vs. SOC will be evaluated using stratified log-rank test.
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. Safety parameters or adverse experiences of special interest that are identified *a priori* constitute "Tier 1" safety endpoints that will be subject to inferential testing for statistical significance with p-values and 95% confidence intervals provided for between-group comparisons. Other safety parameters will be considered Tier 2 or Tier 3. Tier 2 parameters will be assessed via point estimates with 95% confidence intervals provided for between-group comparisons; only point estimates by treatment group are provided for Tier 3 safety parameters. The between-treatment difference will be analysed using the Miettinen and Nurminen method.
Interim Analyses	Two efficacy and one safety interim analyses will be performed in this trial. Results will be reviewed by a DMC. These interim analyses and the final analysis are summarized below. Details are provided in Section 8.7. Safety Interim Analysis • Timing: After 10 subjects in each treatment arm have completed one cycle of follow-up. Interim safety monitoring will include review of AE data by the DMC (see Section 8.6.2 for more details on the analyses methods). Efficacy Interim Analysis ▪ Timing: ▪ Interim analysis 1 (IA1) After: 1) all subjects have been enrolled, 2) minimum of 10 months of follow-up and 3) at least 317 OS events are observed among subjects randomized to the SOC and combination arm with PD-L1 CPS1. ▪ Interim analysis 2 (IA2): 16 months after the last subject is randomized to the trial and after at least 369 OS events are observed among subjects randomized to the SOC and combination arm with PD-L1 CPS1. ▪ Purpose: ▪ IA1: Interim analysis for PFS (PD-L1 CPS1) (H1) and OS (PD-L1 CPS1 and PD-L1 CPS10) (H2-H6). ▪ IA2: Final efficacy analysis for PFS (PD-L1 CPS1) (H1) and interim analysis for OS (PD-L1 CPS1 and PD-L1 CPS10) (H2-H6). Final analysis Timing: at least 22 months after the last subject is randomized to the trial and approximately 415 OS events are observed among subjects randomized to the SOC and combination arm with PD-L1 CPS1.

Multiplicity	The multiplicity strategy specified in Section 8.8 will be applied to the primary hypotheses (PFS [PD-L1 CPS1] [H1] and OS [PD-L1 CPS1 and PD-L1 CPS10]) (H2-H6) and the secondary hypothesis (ORR PD-L1 CPS1) (H7) to control the overall Type-I error at 2.5% (one-sided). The graphical approach of Mauer and Bretz [44] will be used. In this approach, when a particular null hypothesis is rejected, the arrow(s) leading to it are removed, and the Type I error allocated to the null hypothesis that was rejected is re-distributed to the other hypotheses. There are three treatment arms in the study. Initially α=0.10%, 1.25% 0.75% and 0% is allocated to the PFS (PD-L1 CPS1) (H1) , OS(PD-L1 CPS1) (H2), OS (PD-L1 CPS10) (H3) and ORR (PD-L1 CPS1) (H7) hypotheses, respectively, for the Pembrolizumab in combination with SOC versus SOC comparisons and α=0.40%, 0% and 0% is allocate to OS (non-inf PD-L1 CPS1) (H4), OS (PD-L1 CPS1) (H5) and OS (PD-L1 CPS10) (H6) hypotheses, respectively, for the monotherapy vs. SOC (control) comparisons.
Sample Size and Power	The planned sample size is approximately 750 subjects. For PFS (PD-L1 CPS1) (H1), the study has ~91% power to detect a hazard ratio of 0.65 (pembrolizumab in combination with SOC vs. SOC) at alpha = 0.10% (one-sided). For OS (PD-L1 CPS1) (H2), the study has ~91% power to detect a hazard ratio of 0.70 (pembrolizumab in combination with SOC vs. SOC) at alpha = 1.25% (one-sided). For OS (PD-L1 CPS10) (H3), the study has ~80% (73%) power to detect a hazard ratio of 0.58(0.60) (pembrolizumab in combination with SOC vs. SOC) at alpha = 0.75% (one-sided). For the monotherapy vs. SOC comparison of OS (PD-L1 CPS1), the study has ~89% power to establish non-inferiority (H4) (NI margin = 1.2) of pembrolizumab vs SOC at alpha = 0.40% (one-sided) if HR = 0.8 and ~82% power (superiority, H5) to detect a hazard ratio of 0.70 at alpha = 0.40% (one-sided). For OS (PD-L1 CPS10) (H6), the study has ~80%(63%) power to detect a hazard ratio of 0.58(0.63) (pembrolizumab monotherapy vs. SOC) at alpha = 0.75% (one-sided)

8.2 Responsibility for Analyses/In-House Blinding

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

Although the trial is partially blinded (pembrolizumab mono therapy arm open label and pembrolizumab in combination with standard of care and standard of care arms are blinded) analyses or summaries generated by randomized treatment assignment and actual treatment received will be limited and documented. In addition, the independent radiologist(s) will perform the central imaging review without knowledge of treatment group assignment.

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 DMC will serve as the primary reviewer of the unblinded results of the interim analysis and will make recommendations for discontinuation of the study or modification to an

executive oversight committee of the SPONSOR. Depending on the recommendation of the DMC, the Sponsor may prepare a regulatory submission. If the DMC recommends modifications to the design of the protocol or discontinuation of the study, this executive oversight committee and limited additional sponsor personnel may be unblinded to results at the treatment level in order to act on these recommendations. Additional logistical details, revisions to the above plan and data monitoring guidance will be provided in the DMC Charter.

8.3 Hypotheses/Estimation

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

8.4 Analysis Endpoints

Primary Efficacy Endpoints

Progression-free survival (PFS) – RECIST 1.1 by blinded central radiologists' review

PFS is defined as the time from randomization to the first documented disease progression per RECIST 1.1 based on blinded central radiologists' review or death due to any cause, whichever occurs first. See Section 8.6.1 for definition of censoring.

Overall Survival (OS)

OS 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.

Secondary Efficacy Endpoint

Overall Response Rate (ORR) – RECIST 1.1 by blinded central radiologists' review

ORR is defined as the proportion of the subjects in the analysis population who have a CR or partial response (PR).

8.5 ANALYSIS POPULATIONS

8.5.1 Efficacy Analysis Populations

The Intention-to-Treat (ITT) 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. 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 analysed 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 one laboratory or vital sign measurement obtained subsequent to at least one dose of study treatment is required for inclusion in the analysis of each specific parameter. To assess change from baseline, a baseline measurement is also required.

8.6 STATISTICAL METHODS

8.6.1 Statistical Methods for Efficacy Analyses

This section describes the statistical methods that address the primary and secondary objectives. Methods related to exploratory objectives and exploratory endpoints will be described in the supplemental statistical analysis plan (sSAP), this includes the ePRO data described in Section 7.1.2.9.

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 and Section 8.7 Interim Analysis. Nominal p-values will be provided for other efficacy analyses, but should be interpreted with caution due to potential issues of multiplicity.

Progression-free Survival (PFS)

The non-parametric Kaplan-Meier method will be used to estimate the PFS curve in each treatment group. The treatment difference in PFS will be assessed by the stratified log-rank test. A stratified Cox proportional hazards model with Efron’s method of tie handling will be used to assess the magnitude of the treatment difference (ie, hazard ratio) between the treatment arms. The hazard ratio and its 95% confidence interval from the stratified Cox model with Efron's method of tie handling and with a single treatment covariate will be reported. Geographic region, backbone therapy (5-FU or Capecitabine) and disease status will be used as the stratification factors in both the stratified log-rank test and the stratified Cox model.

Since disease progression is assessed periodically, PD can occur any time in the time interval between the last assessment where PD was not documented and the assessment when PD is documented. For the primary analysis, for the subjects who have PD, the true date of disease progression will be approximated by the date of the first assessment at which PD is

objectively documented per RECIST 1.1, regardless of discontinuation of study drug. Death is always considered as a confirmed PD event. Subjects without documented PD/death will be censored at the last disease assessment date.

In order to evaluate the robustness of the primary endpoint PFS per RECIST 1.1 by blinded central radiologists' review, we will perform two sensitivity analyses with a different set of censoring rules. The first sensitivity analysis is the same as the primary analysis except that it censors at the last disease assessment without PD when PD or death is documented after more than one missed disease assessment. The second sensitivity analysis is the same as the primary analysis except that it considers discontinuation of treatment or initiation of an anticancer treatment subsequent to discontinuation of study-specified treatments, whichever occurs later, to be a PD event for subjects without documented PD or death. The censoring rules for primary and sensitivity analyses are summarized in Table 12 below.

Table 12 Censoring Rules for Primary and Sensitivity Analyses of PFS

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

Overall Survival (OS)

The non-parametric Kaplan-Meier method will be used to estimate the survival curve**s**. The treatment difference in survival will be assessed by the stratified log-rank test for superiority hypotheses. A stratified Cox proportional hazards model with Efron's method of tie handling will be used to assess the magnitude of the treatment difference (ie, the hazard ratio). The hazard ratio and its 95% confidence interval from the stratified Cox model with a single treatment covariate will be reported. Geographic region, backbone therapy (5-FU or

Capecitabine) and disease status will be used as the stratification factors in both the stratified log-rank test and the stratified Cox model.

The non-inferiority hypothesis (H4) for pembrolizumab monotherapy vs. SOC will be evaluated using a stratified Cox regression model. The statistical criterion for the success of hypothesis H4 is that, if the upper bound of the confidence interval, based on the alpha level allocated to the analysis, for the hazard ratio (HR: monotherapy arm vs. control) is < 1.2, the pembrolizumab monotherapy arm could be considered as non-inferior to the control arm in terms of OS.

Overall Response Rate (ORR)

Stratified Miettinen and Nurminen's method with strata weighting by sample size will be used for comparison of the ORR between the treatment groups. Geographic region, backbone therapy (5-FU or Capecitabine) and disease status will be used as the stratification factors in the analysis.

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

Table 13 Analysis Strategy for Key Efficacy Endpoints

Endpoint/Variable (Description, Time Point)	Statistical Method†	Analysis Population	Missing Data Approach
Primary Endpoints			
PFS per RECIST 1.1 by blinded central radiologists' review	Testing: Stratified Log-rank test. Estimation: Stratified Cox model with Efron's tie handling method	ITT	• Primary censoring rule • Sensitivity analysis 1 • Sensitivity analysis 2 (More details in Table 12)
OS	Testing: Stratified Log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT	Censored at last date known alive
Secondary Endpoint			
ORR Per RECIST 1.1 by blinded central radiologists' review	Stratified Miettinen and Nurminen method	ITT	Subjects with missing data are considered non-responders
† Statistical models are described in further detail in the text. For stratified analyses, Geographic region, backbone therapy and disease status will be used as the stratification factors in both the stratified log-rank test and the stratified Cox model.			

8.6.2 Statistical Methods for Safety Analyses

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

The analysis of safety results will follow a tiered approach (Table 14). The tiers differ with respect to the analyses that will be performed. Safety parameters or adverse experiences of special interest that are identified *a priori* constitute "Tier 1" safety endpoints that will be subject to inferential testing for statistical significance with p-values and 95% confidence intervals provided for between-group comparisons. Other safety parameters will be considered Tier 2 or Tier 3. Tier 2 parameters will be assessed via point estimates with 95% confidence intervals provided for between-group comparisons; only point estimates by treatment group are provided for Tier 3 safety parameters.

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

The threshold of at least 4 events was chosen because the 95% confidence interval for the between-group difference in percent incidence will always include zero when treatment groups of equal size each have less than 4 events and thus would add little to the interpretation of potentially meaningful differences. Because many 95% confidence intervals may be provided without adjustment for multiplicity, the confidence intervals should be regarded as a helpful descriptive measure to be used in review, not a formal method for assessing the statistical significance of the between-group differences in adverse experiences and predefined limits of change.

Continuous measures such as changes from baseline in laboratory, vital signs, and ECG parameters that are not pre-specified as Tier-1 endpoints will be considered Tier 3 safety parameters. Summary statistics for baseline, on-treatment, and change from baseline values will be provided by treatment group in table format.

Based on a review of historic chemotherapy data and data from ongoing pembrolizumab clinical trials in gastric cancer, there are no AEs of interest that warrant inferential testing for comparison between treatment arms in this study. Therefore, there are no Tier I events in this study. The broad clinical and laboratory AE categories consisting of the percentage of subjects with any AE, any drug related AE, any serious AE, any Grade 3-5 AE, an AE which is both Grade 3-5 and drug-related, an AE which is both drug-related and serious, dose modification due to AE, and who discontinued due to an AE, and death will be considered Tier 2 endpoints. Ninety Five percent (95%) confidence intervals Tier 2) will be provided for between-treatment differences in the percentage of subjects with events; these analyses will be performed using the Miettinen and Nurminen method (1985), an unconditional, asymptotic method.

Table 14 Analysis Strategy for Safety Parameters

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

8.6.3 Statistical Methods for Patient Reported Outcome (PRO) Analyses: EORTC QLQ-C30 and EORTC QLQ-STO22

Changes in health-related quality-of-life assessments from baseline using the EORTC QLQ-C30 and EORTC QLC-STO22 will be evaluated using a constrained longitudinal data analysis (cLDA) model.

Time to deterioration (10 points worse than baseline) in EORTC QLQ-C30 global health status, nausea/vomiting symptom, appetite loss symptom, and QLQ-STO22 abdominal pain/discomfort symptom will be analysed using the same methods used for the primary endpoint, PFS (stratified Cox model and Kaplan Meier plot). Rate of improvement (10 points better than baseline) for these endpoints will be analysed using the same method used for ORR (ie stratified Miettinen and Nurminen's method).

Details of PRO analyses will be described in the sSAP.

8.6.4 Summaries of Baseline Characteristics, Demographics, and Other Analyses

8.6.4.1 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 randomized, and the primary reason for discontinuation will be displayed. Demographic variables (such as age) and baseline

characteristics will be summarized by treatment either by descriptive statistics or categorical tables.

8.7 INTERIM ANALYSES

8.7.1 Safety Interim Analysis

An interim safety analysis will take place after 10 subjects in each treatment arm have completed 1 cycle of therapy. Interim periodic safety monitoring will include review of AE data by the eDMC as specified in the DMC charter.

8.7.2 Efficacy Interim Analyses

There are two interim analyses planned in this study. The first interim analysis (IA1) will take place when all subjects are enrolled and followed for 10 months and at least 317 OS events are observed across the pembrolizumab in combination with SOC and SOC arms, in subjects with PD-L1 CPS1. The second interim analysis (IA2) will take place after a minimum of 16 months follow-up and at least 369 OS events are observed across the pembrolizumab in combination with SOC and SOC arms, in subjects with PD-L1 CPS1. In order to account for potential delayed treatment effect, which was observed with immunotherapy study data external to this study, the final analysis (FA) will be 22 months after the last subject is randomized and approximately 415 OS events are observed across the pembrolizumab in combination with SOC and SOC arms, in subjects with PD-L1 CPS1 [48; 49; 50]. The additional follow-up time is incorporated into the trial to ensure that the final analysis is conducted at an appropriate time to characterize the potential benefit of immunotherapy, where the treatment effect is most pronounced towards the tail of the survival curve. Table 15 summarizes the key features of the interim analysis.

For PFS (H1) and OS (H2, H3, H5, and H6), a Hwang-Shih-DeCani alpha-spending function with gamma parameter (-4) is used to construct group sequential boundaries to control the type I error rate. For OS (H4 – NI monotherapy vs. SOC in the CPS1 population), a Hwang-Shih-DeCani alpha-spending function with gamma parameter (-15) is used to construct group sequential boundaries to control the type I error rate.

For H2, the actual boundaries and the alpha level will be determined from the number of events observed at the time of the interim analyses using the corresponding alpha-spending function. The boundary for the final analysis will be adjusted according to the actual alpha spent at the IAs and the actual number of events observed at the IA and FA.

For H1, H3, H4, H5, and H6, since the timing of the IAs are not driven by these hypotheses; alpha is spent as a function of the minimum of the actual event information fraction and the expected event information fraction. This 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. If events accrue more slowly than expected or the same as expected, spending will be based on actual information fraction. If events accrue more quickly than expected, cumulative spending based on the expected information fraction will be used in order to save some alpha for analyses that will be performed with more than the

originally planned maximum events. For example, at IA1 for H3, if 125 OS events have occurred (ie, more than the expected 111 OS events), the alpha spending at IA1 will be according to the expected information fraction (111/147 = 76%) instead of the actual information fraction (125/147 = 85%).

Table 15 summarizes the timing, sample size, and decision guidance of the interim analyses and FA. Bounds are based on estimated number of events and the alpha allocated at the design stage of the study and will be updated at the time of the analyses using the observed number of events, the alpha re-allocation and spending functions as noted above.

Table 15 Decision Guidance at Each Efficacy Analysis

Analysis	Criteria for Conduct of Analysis	Testing	Value	Efficacy
Interim Analysis 1 (Interim OS analysis/ PFS analysis)	10 months after last subject randomized and at least 317 OS events in the combination arm and SOC arm, in subjects with PD-L1 CPS1 whichever comes later	PFS (H1) : pembrolizumab in combination with SOC vs. SOC, in subjects with PD-L1 CPS1	p value (1-sided)	≤0.0007
			~ HR at bound (~ 389 events)	0.723
		OS (H2): Pembrolizumab in combination with SOC vs. SOC in subjects with PD-L1 CPS1	p value (1-sided)	≤0.0047
			~ HR at bound (~317 events)	0.747
		OS (H3): Pembrolizumab in combination with SOC vs. SOC in subjects with PD-L1 CPS10	p value (1-sided)	<=0.0027
			~ HR at bound (~111 events)	0.590
		OS (H4): Non-inferiority of Pembrolizumab mono therapy vs. SOC in subjects with PD-L1 CPS1	p value (1-sided)	≤0.0001
			~ HR at bound (~ 317 events)	0.7935
		OS (H5): Pembrolizumab mono therapy vs. SOC in subjects with PD-L1 CPS1	p value (1-sided)	≤ 0.0015
			~ HR at bound (~ 317 events)	0.717
		OS (H6): Pembrolizumab mono therapy vs. SOC, in subjects with PD-L1 CPS10	p value (1-sided)	≤0.0027
			~ HR at bound (~ 112 events)	0.592

Analysis	Criteria for Conduct of Analysis	Testing	Value	Efficacy
Interim Analysis 2 (Interim OS analysis/ Final PFS analysis)	16 months after the last subject is randomized and at least 369 OS events are observed in the Combination arm and SOC arm, whichever comes later	PFS (H1): pembrolizumab in combination with SOC vs. SOC, in subjects with PD-L1 CPS1	p value (1-sided)	≤0.0007
			~ HR at bound (~430 events)	0.735
		OS (H2): Pembrolizumab in combination with SOC vs. SOC, in subjects with PD-L1 CPS1	p value (1-sided)	≤0.0063
			~ HR at bound (~ 369 events)	0.771
		OS (H3): Pembrolizumab in combination with SOC vs. SOC, in subjects with PD-L1 CPS10	p value (1-sided)	≤0.0037
			~ HR at bound (~130 events)	0.624
		OS (H4) Non-inferiority: Pembrolizumab vs. SOC, in subjects with PD-L1 CPS1	p value (1-sided)	≤0.0007
			~ HR at bound (~ 369 events)	0.862
		OS (H5) superiority: Pembrolizumab vs. SOC, in subjects with PD-L1 CPS1	p value (1-sided)	≤0.0019
			~ HR at bound (~ 369 events)	0.740
		OS (H6) superiority: Pembrolizumab vs. SOC, in subjects with PD-L1 CPS10	p value (1-sided)	≤0.0037
			~ HR at bound (~ 131 events)	0.626

Analysis	Criteria for Conduct of Analysis	Testing	Value	Efficacy
Final Analysis: OS analysis	22 months after the last subject is randomized and approximate 415 OS events are observed in the combination arm and SOC arm, in subjects with PD-L1 CPS1.	OS (H2): Pembrolizumab in combination with SOC vs. SOC, in subjects with PD-L1 CPS1.	p value (1-sided)	≤0.0099
			~ HR at bound (~ 415 events)	0.795
		OS (H3) Pembrolizumab in combination with SOC vs. SOC, in subjects with PD-L1 CPS10	p value (1-sided)	≤0.0058
			~ HR at bound (~ 147 events)	0.659
		OS (H4) non-inferiority pembrolizumab mono therapy vs. SOC, in subjects with PD-L1 CPS1	p value (1-sided)	≤0.0039
			HR at bound (~ 415 events)	0.925
		OS (H5) superiority: Pembrolizumab vs. SOC, in subjects with PD-L1 CPS1	p value (1-sided)	≤0.003
			~ HR at bound (~415 events)	0.763
		OS (H6) superiority: Pembrolizumab vs. SOC, in subjects with PD-L1 CPS10	p value (1-sided)	≤0.0058
			~ HR at bound (~ 148 events)	0.661

For ORR, the analysis population is subjects with 10 months follow up. Based on the current timing of IA1, all subjects will have 10 months follow-up by IA1. Interim analysis 1 will be the final analysis for ORR (H7).

8.8 Multiplicity

The multiplicity strategy specified in this section will be applied to the primary hypotheses PFS(H1) and OS(H2, H3, H4, H5, H6) and the secondary hypothesis ORR(H7) to control the overall Type-I error at 2.5% (one-sided). The graphical approach of Mauer and Bretz [44] is followed.

Figure 2 provides the multiplicity strategy diagram of the trial. In this approach, when a particular null hypothesis is rejected, the arrow(s) leading to it are removed, and the Type I error allocated to the null hypothesis that was rejected is re-distributed to the other hypotheses.

There are three treatment arms in the study. Initially α=0.1%, 1.25%, 0.75% and 0% is allocated to the PFS-PD-L1 CPS1 (H1), OS-PD-L1 CPS1 (H2), OS- PD-L1 CPS10 (H3) and ORR- PD-L1 CPS1 (H7) hypotheses, respectively for the Pembrolizumab in combination

with SOC versus SOC comparisons and α=0.4% is allocated to the non-inferiority hypothesis of monotherapy vs. SOC (control)- OS non-inf PD-L1 CPS1 (H4).

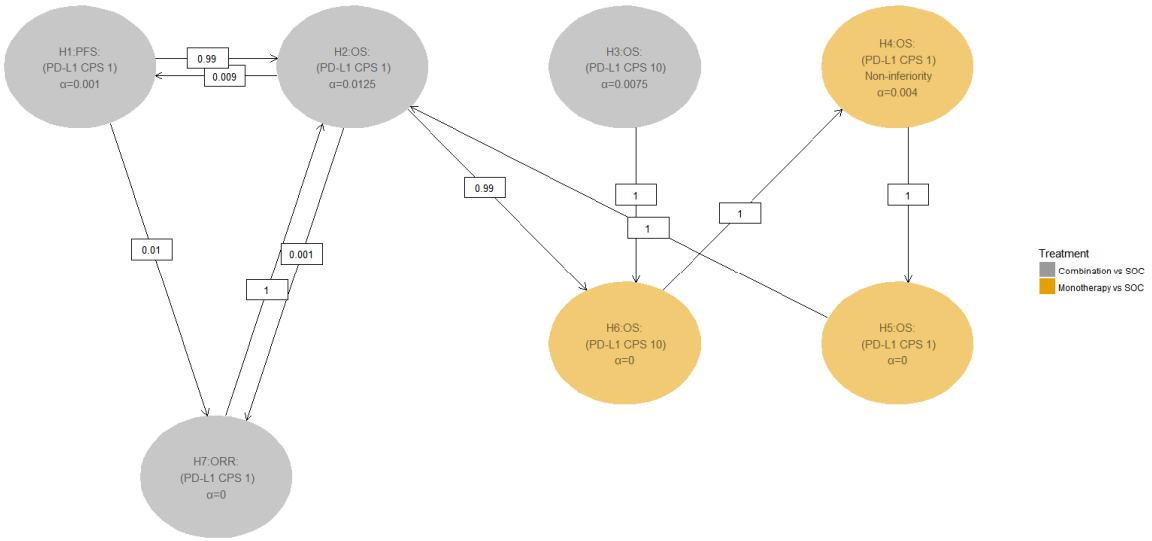


Figure 2 Multiplicity Strategy

8.9 Sample Size and Power Calculations

The study will randomize approximately 750 subjects in a 1:1:1 ratio among the three treatment arms: pembrolizumab as monotherapy (mono therapy), pembrolizumab in combination with SOC (combination therapy), and SOC (control).

The study is event driven (ie, follow-up times are subject to change but number of events is not).

PFS:

At the final PFS-PD-L1 CPS1 (H1) analysis (IA2), approximately 16 months after the last subject is randomized approximately 430 PFS events will be accumulated in the combination therapy arm and control arm. With 430 events, the study has ~91% power to detect a hazard ratio of 0.65 (pembrolizumab in combination with SOC vs. SOC) at alpha = 0.10% (one-sided). The sample size calculation is based on the following assumptions: 1) progression-free survival follows an exponential distribution with a median of 6 months in the control arm, 2) an enrollment period of 19 months, and 3) a yearly dropout rate of 5%.

OS:

At the FA, approximately 415 OS PD-L1 CPS1 (H2) events will be accumulated in the combination therapy arm and control arm. With 415 events, the study has ~91% power to detect a hazard ratio of 0.70 (pembrolizumab in combination with SOC vs. SOC) at alpha = 1.25% (one-sided). These calculations are based on the following assumptions: 1) OS follows an exponential distribution with a median of 10 months in the control arm, 2) an enrolment period of 19 months, and 3) a yearly dropout rate of 2%.

At the final analysis, approximately 147 OS-PD-L1 CPS10 (H3) events will be accumulated in the combination therapy arm and control arm. With 147 events, the study has ~ 80% (73%) power to detect a hazard ratio of 0.58(0.60) (pembrolizumab in combination with SOC vs. SOC in subgroup of subjects with PD-L1 CPS10) at alpha = 0.75% (one-sided)

For the monotherapy arm and the control arm, if there are 415 OS PD-L1 CPS1 events, the study has ~89% power to establish non-inferiority (H4) (NI margin =1.2) of pembrolizumab vs SOC (H4) at alpha=0.40% (one-sided) if HR = 0.82, and ~82% power (superiority, H5) to detect a HR = 0.70 at alpha = 0.40%. Following the FDA Guidance for Non-Inferiority Clinical Trials [52], the non-inferiority margin was based on retaining 50% of the control effect size (cisplatin and 5-fluorouracil vs. BSC), ie the lower bound of the confidence interval of the estimated control effect based on past studies. The control effect size is estimated as 0.67 based on Wagner 2006 [53]

At the final analysis, approximately 148 OS-PD-L1 CPS10 (H6) events will be accumulated in the pembrolizumab and control arm. With 148 events, the study has ~ 80% (63%) power to detect a hazard ratio of 0.58(0.63) (pembrolizumab vs. SOC in subgroup of subjects with PD-L1 CPS10) at alpha = 0.75% (one-sided)

The assumed median PFS and OS in the control arm are observed from standard of care in 1L treatment of gastric cancer [45] [46].

The sample size and power calculations were performed in the software EAST 5.4.

8.10 Subgroup Analyses and Effect of Baseline Factors

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

- Stratification factors
    - Geographic region of enrolling site (US and EU, ROW, Asia).
    - Disease Status: Locally advanced vs metastatic
    - Backbone therapy (5-FU vs. Capecitabine)

- Age category (≤65 vs. >65 years)
- Sex (female vs. male)
- ECOG status (0 vs. 1)
- Primary location: Stomach vs GEJ
- Histological subtype: Diffuse vs intestinal vs mixed
- Tumor Burden (above and below median)
- Number of metastasis: ≤2 vs ≥3
- Prior Gastrectomy: yes vs no

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 16.

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 16 Product Descriptions

Product Name & Potency	Dosage Form	Additional Information
Pembrolizumab (MK-3475), 25 mg/mL	Injection	Provided centrally by the Sponsor
Cisplatin, 1 mg/mL	Injection	Provided centrally by the Sponsor or locally by the trial site, subsidiary, or designee
Fluorouracil (5-FU), 50 mg/mL	Injection	Provided centrally by the Sponsor or locally by the trial site, subsidiary, or designee
Capecitabine 150mg and 500 mg	Tablet	Provided centrally by the Sponsor or locally by the trial site, subsidiary, or designee

All supplies indicated in Table 16 will be provided per the "Additional Information" field depending on local country operational or regulatory requirements.

Any commercially available product not included in Table 16 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 to record 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.

Study sites will receive open label MK-3475 vials and open label cisplatin and fluorouracil kits. Each kit will contain 1 commercial vial.

Study sites supplied with capecitabine centrally from the Sponsor will receive kit boxes containing 60 tablets of the 150 mg strength and kit boxes containing 120 tablets of the 500 mg strength.

9.3 Clinical Supplies Disclosure

Treatment Arm 1 (pembrolizumab monotherapy) of the trial is open-label; therefore, the subject, the trial site personnel, the Sponsor and/or designee are not blinded. Treatment (name, strength or potency) is included in the label text; random code/disclosure envelopes or lists are not provided.

Treatment in Arms 2 and 3 (pembrolizumab+chemotherapy and placebo+chemotherapy, respectively) of the trial is blinded but 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 Treatment in Arms 2 and 3 (pembrolizumab+ chemotherapy and placebo+ chemotherapy, respectively) of the trial]. 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.

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

In the event that unblinding has occurred, the circumstances around the unblinding (e.g., date and reason) 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 subject.

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

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

10.1 Confidentiality

10.1.1 Confidentiality of Data

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

10.1.2 Confidentiality of Subject Records

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

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

10.1.3 Confidentiality of Investigator Information

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

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

2. hospital or clinic address and telephone number;

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

4. other professional documentation.

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

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

10.1.4 Confidentiality of IRB/IEC Information

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

10.2 Compliance with Financial Disclosure Requirements

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

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

10.3 Compliance with Law, Audit and Debarment

By signing this protocol, the investigator agrees to conduct the trial in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of Good Clinical Practice (e.g., International Conference on Harmonization of Technical

Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice: Consolidated Guideline and other generally accepted standards of good clinical practice); and all applicable federal, state and local laws, rules and regulations relating to the conduct of the clinical trial.

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

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

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

The investigator shall prepare and maintain complete and accurate trial documentation in compliance with Good Clinical Practice standards 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 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 collected in this trial as outlined in Section 7.1.3.3 – Future Biomedical Research will be used to study various causes for how subjects may respond to a drug/vaccine. Future biomedical research specimen(s) will be stored to provide a resource for future trials conducted by Merck focused on the study of biomarkers responsible for how a drug/vaccine enters and is removed by the body, how a drug/vaccine works, other pathways a drug/vaccine may interact with, or other aspects of disease. The specimen(s) may be used for future assay development and/or drug/vaccine development.

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

3. Summary of Procedures for Future Biomedical Research

a. Subjects for Enrollment

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

b. Informed Consent

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

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

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

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

c. eCRF Documentation for Future Biomedical Research Specimens

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

d. Future Biomedical Research Specimen Collections

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

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

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

4. Confidential Subject Information for Future Biomedical Research

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

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

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

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

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

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

5. Biorepository Specimen Usage

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

Analyses utilizing the Future Biomedical Research specimens may be performed by Merck, or an additional third party (e.g., a university investigator) designated by Merck. The investigator conducting the analysis will be provided with double coded specimens. Re-association of analysis results with corresponding clinical data will only be conducted by the Merck Entrusted Keyholder. Any contracted third party analyses will conform to the specific scope of analysis outlined in this sub-trial. Future Biomedical Research specimens remaining with the third party after the specific analysis is performed will be

returned to the sponsor or destroyed and documentation of destruction will be reported to Merck.

6. Withdrawal From Future Biomedical Research

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

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

7. Retention of Specimens

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

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

8. Data Security

Separate databases for specimen information and for results from the Future Biomedical Research sub-trial will be maintained by Merck. This is done to separate the future exploratory test results (which include genetic data) from the clinical trial database thereby maintaining a separation of subject number and these results. The separate databases are accessible only to the authorized Sponsor and the designated trial administrator research personnel and/or collaborators. Database user authentication is highly secure, and is accomplished using network security policies and practices based in international standards (e.g., ISO17799) to protect against unauthorized access. The Merck Entrusted Keyholder maintains control over access to all specimen data. These

data are collected for future biomedical research purposes only as specified in this sub-trial will not be used for any other purpose.

9. Reporting of Future Biomedical Research Data to Subjects

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

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

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

10. Gender, Ethnicity and Minorities

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

11. Risks Versus Benefits of Future Biomedical Research

For future biomedical research, risks to the subject have been minimized. No additional risks to the subject have been identified as no additional specimens are being collected for Future Biomedical Research (ie, only leftover samples are being retained

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

It is necessary for subject-related data (i.e., ethnicity, diagnosis, drug therapy and dosage, age, toxicities, etc.) to be re-associated to double coded specimens at the time of data analysis. These subject data will be kept in a separate, secure Merck database, and all

specimens will be stripped of subject identifiers. No information concerning results obtained from future biomedical research will be entered into clinical records, nor will it be released to outside persons or agencies, in any way that could be tied to an individual subject.

12. Self-Reported Ethnicity

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

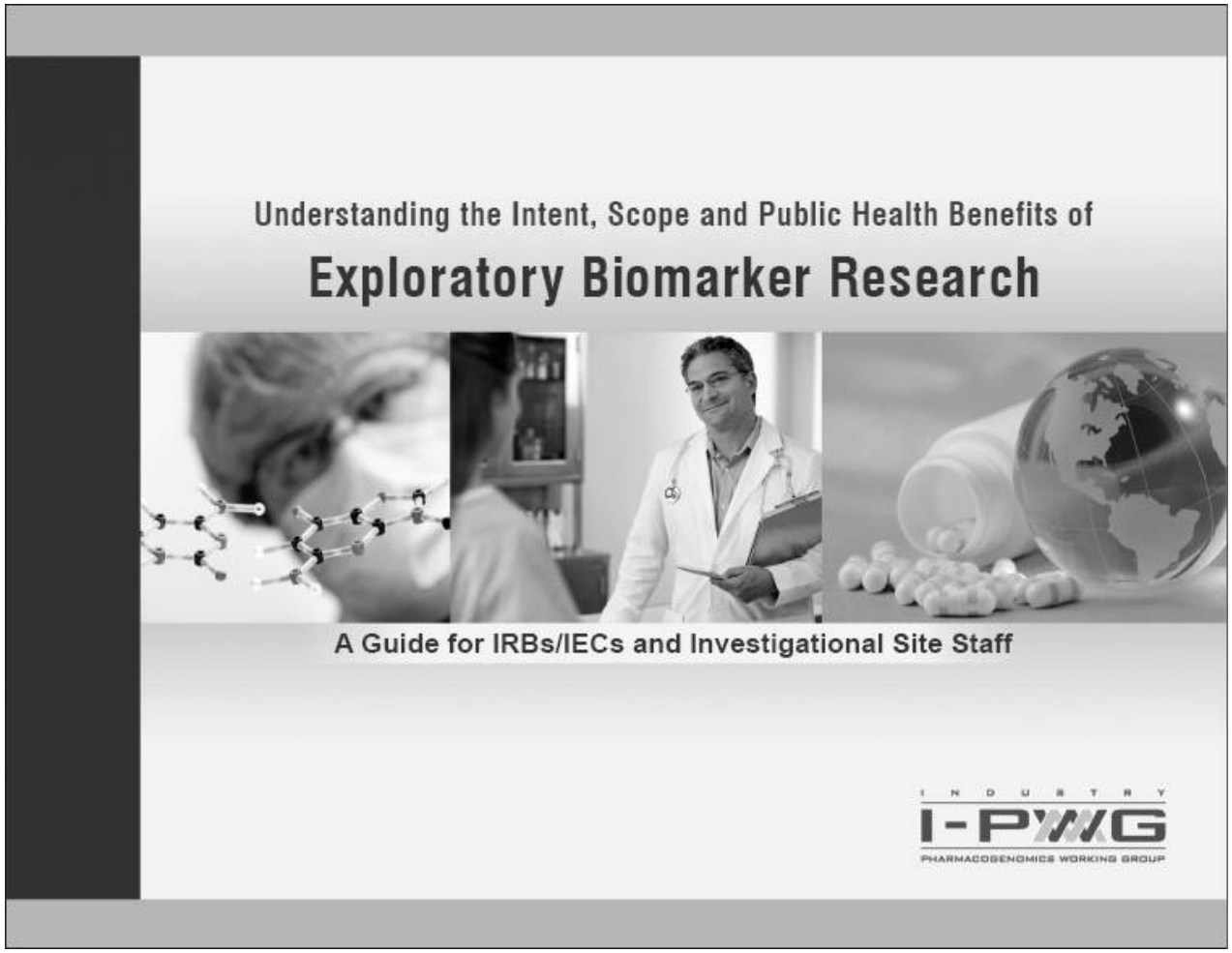
13. Questions

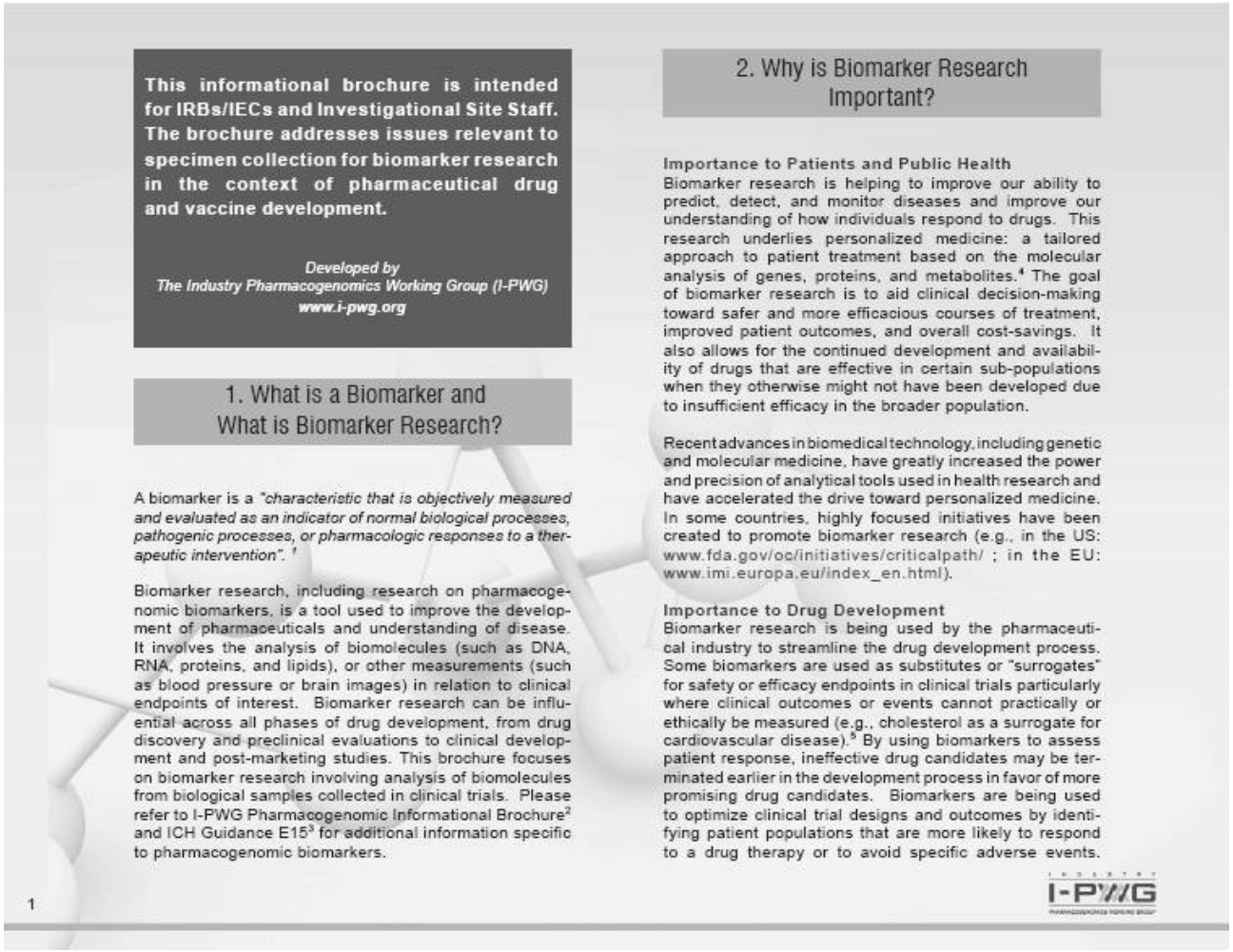
Any questions related to the future biomedical research should be e-mailed directly to clinical.specimen.management@merck.com.

14. References

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

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





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

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

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

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

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

2. Why is Biomarker Research Important?

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

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

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

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

3. Importance of Biomarkers to Regulatory Authorities

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

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

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

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

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

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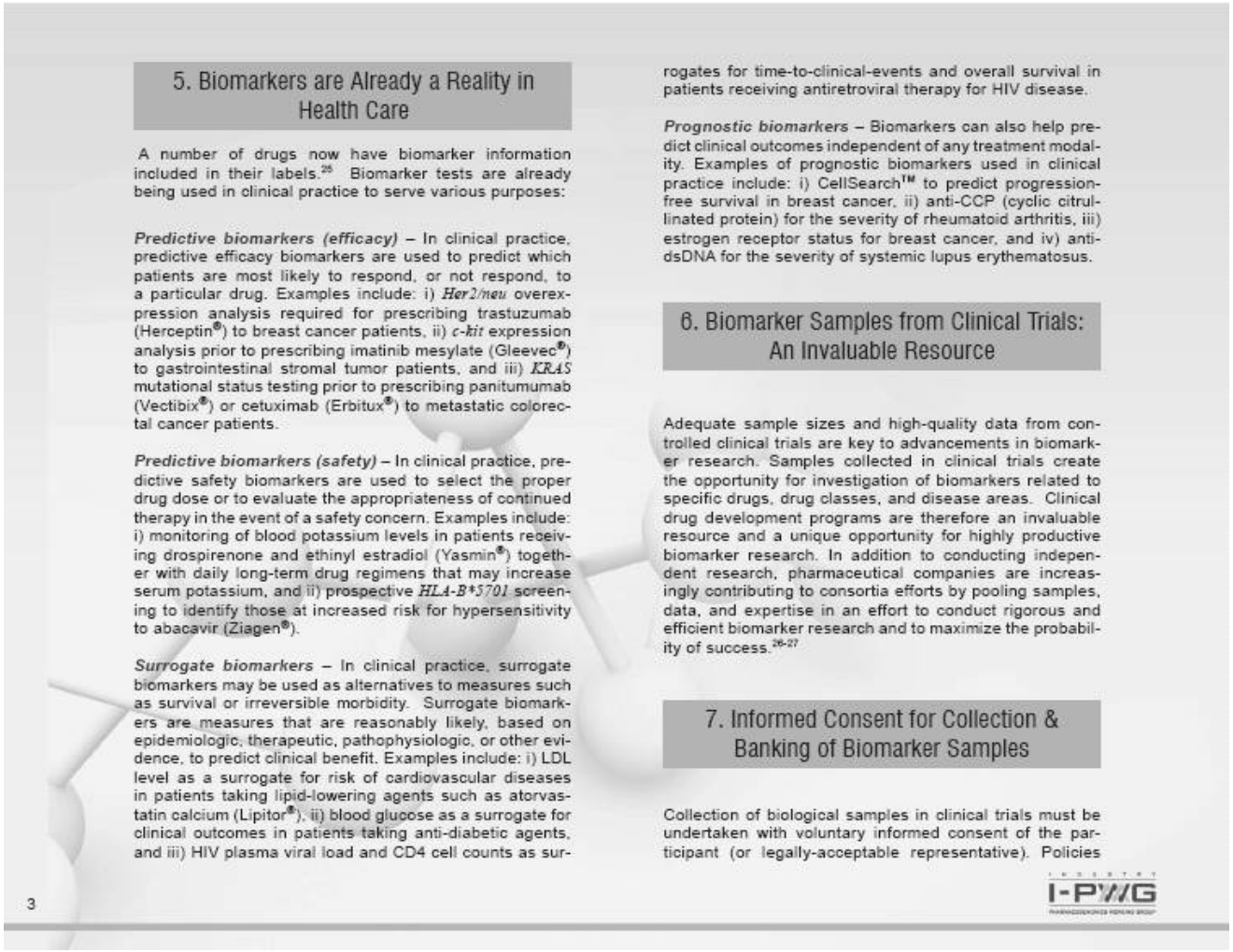

5. Biomarkers are Already a Reality in Health Care

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

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

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

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

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

6. Biomarker Samples from Clinical Trials: An Invaluable Resource

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

7. Informed Consent for Collection & Banking of Biomarker Samples

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

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

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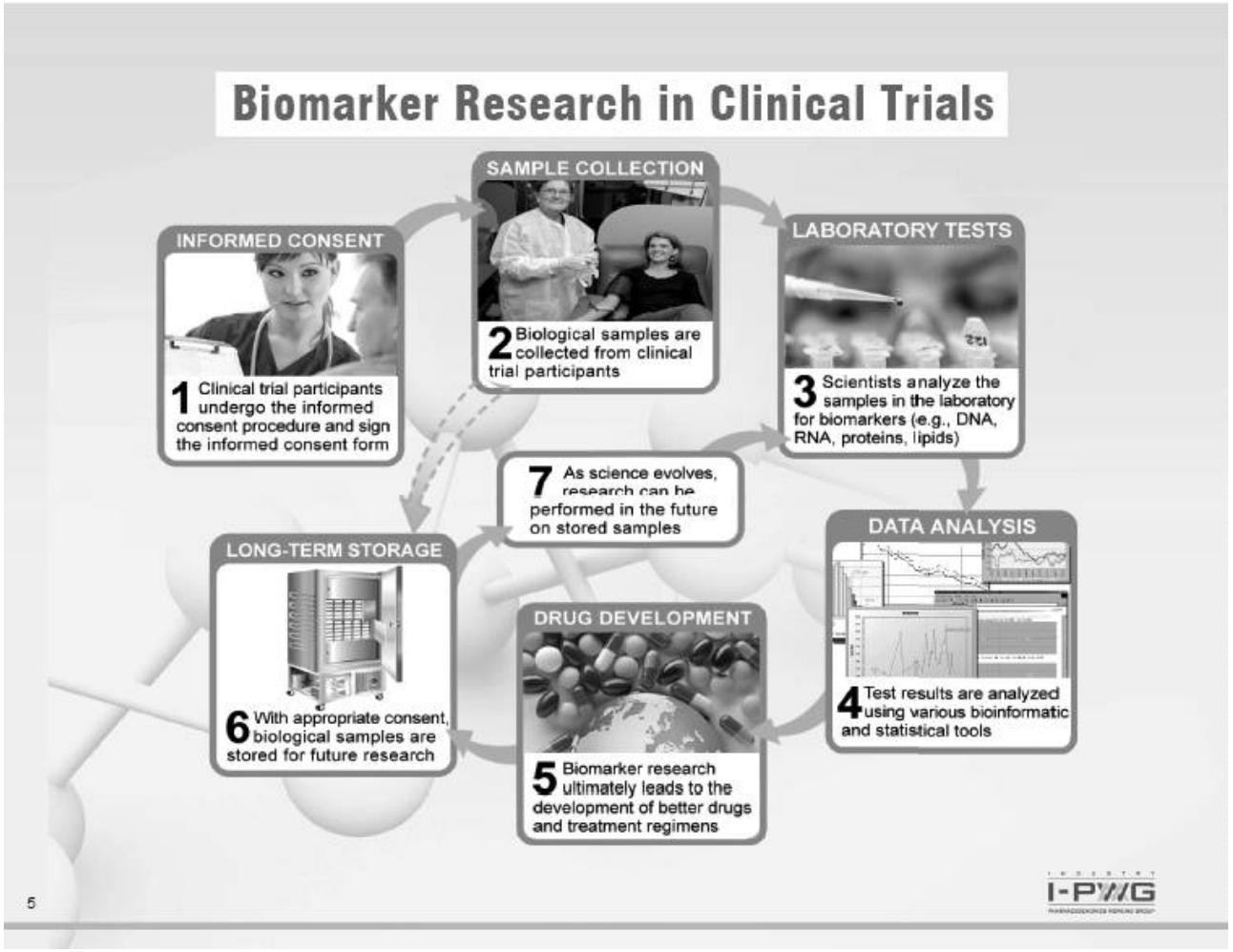
Biomarker Research in Clinical Trials
SAMPLE COLLECTION
2 Biological samples are collected from clinical trial participants
LABORATORY TESTS
3 Scientists analyze the samples in the laboratory for biomarkers (e.g., DNA, RNA, proteins, lipids)
INFORMED CONSENT
1 Clinical trial participants undergo the informed consent procedure and sign the informed consent form
7 As science evolves, research can be performed in the future on stored samples
DATA ANALYSIS
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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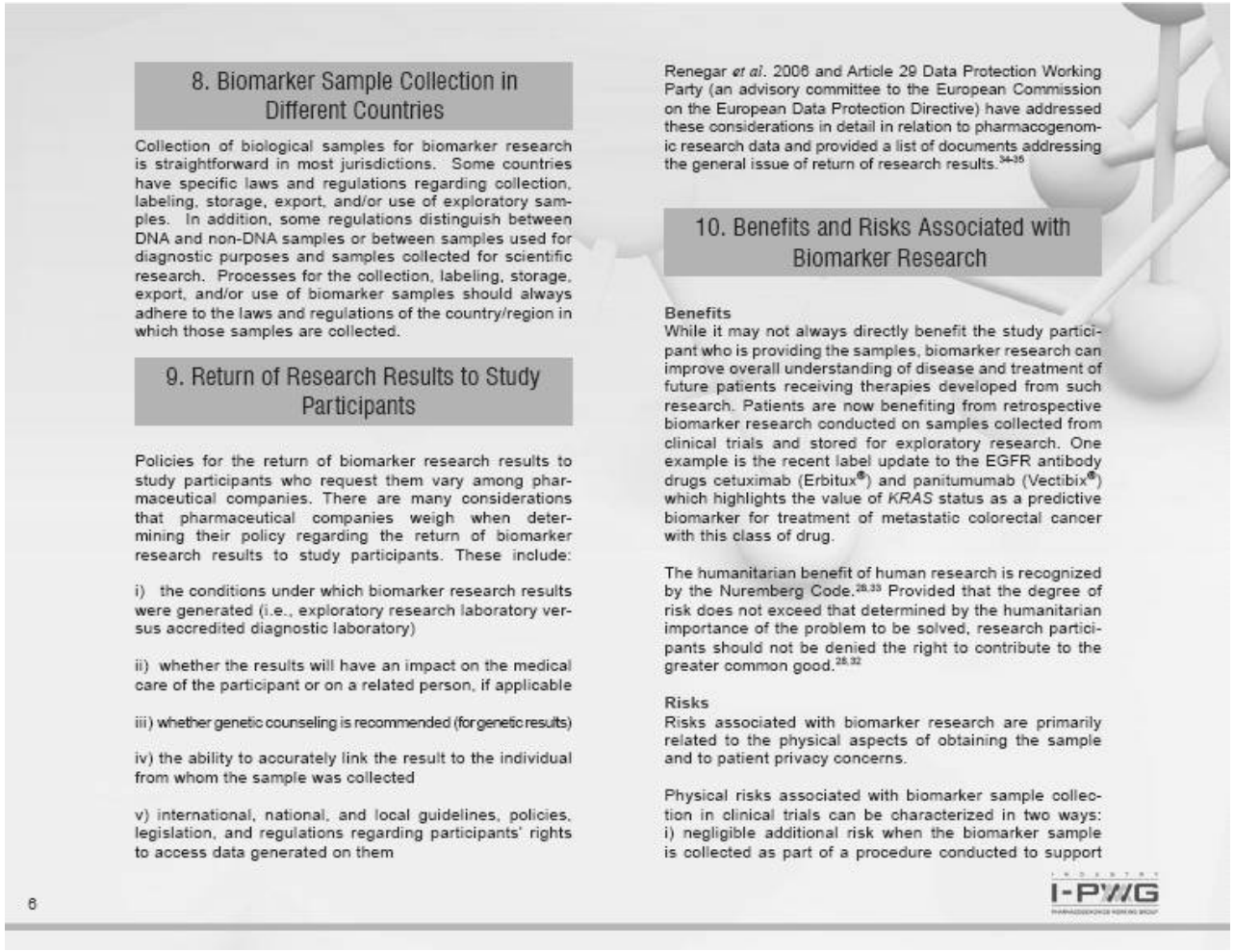

8. Biomarker Sample Collection in Different Countries

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

10. Benefits and Risks Associated with Biomarker Research

Benefits

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

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

Risks

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

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

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

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

11. Privacy, Confidentiality, and Patient Rights

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

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

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

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

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

12.Where to Get More Information?

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

13. What is I-PWG?

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

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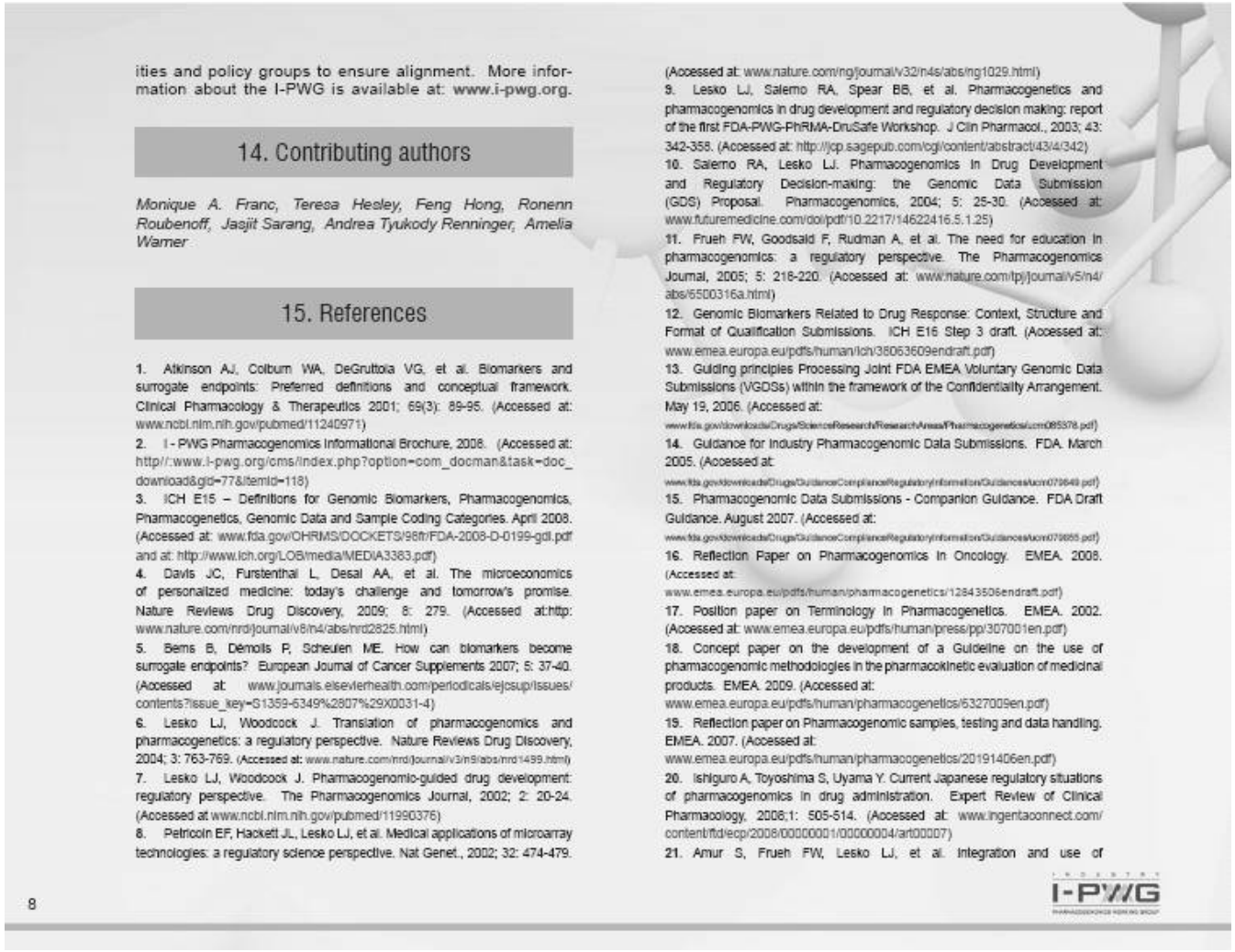

ities and policy groups to ensure alignment. More information about the I-PWG is available at: www.i-pwg.org.

14. Contributing authors

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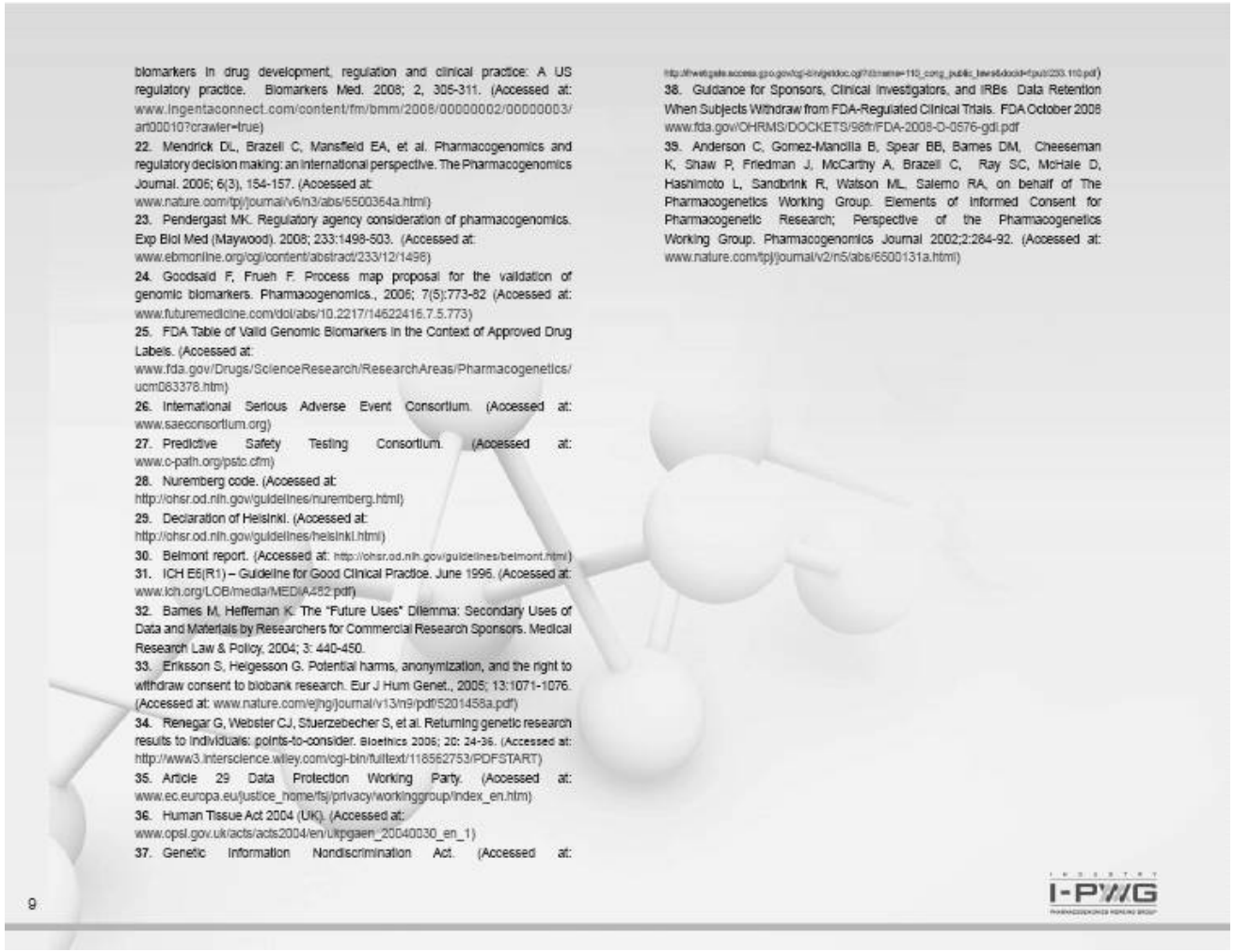

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12.4 ECOG Performance Status

GRADE	ECOG PERFORMANCE STATUS
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 a light or sedentary nature, eg, light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Dead

*Oken M, Creech R, Tormey D, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol.* 1982;5:649-655

http://ecog-acrin.org/resources/ecog-performance-status

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

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

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

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

* As published in the European Journal of Cancer [46].

12.7 Dose Modification Table (based on modified Toxicity Profile Interval [33]

Sample size = 40[a]; Target probability p_T = 30%; $\varepsilon_1 = \varepsilon_2 = 0.05$.

Any doses with a dose reduction probability falling into the interval ($pT - \varepsilon 1$, $pT + \varepsilon 2$) will be considered an acceptable dose level.

Number of Toxicity	Number of Patients																	
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
0	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E
1	D	S	S	S	S	E	E	E	E	E	E	E	E	E	E	E	E	E
2		D	D	S	S	S	S	S	S	S	E	E	E	E	E	E	E	E
3			D	D	D	S	S	S	S	S	S	S	S	S	S	E	E	E
4				D	D	D	D	D	S	S	S	S	S	S	S	S	S	S
5					D	D	D	D	D	D	S	S	S	S	S	S	S	S
6						D	D	D	D	D	D	D	S	S	S	S	S	S
7							D	D	D	D	D	D	D	D	S	S	S	S
8								D	D	D	D	D	D	D	D	D	D	S
9									D	D	D	D	D	D	D	D	D	D
10										D	D	D	D	D	D	D	D	D
11											D	D	D	D	D	D	D	D
12												D	D	D	D	D	D	D
13													D	D	D	D	D	D
14														D	D	D	D	D
15															D	D	D	D
16																D	D	D
17																	D	D
18																		D

LEGEND

E: Stay at same dose or escalate to the next higher dose (escalation will only apply if the initial dose has been lowered, as doses higher than 800 mg/m^2 for 5-FU and 80 mg/m^2 for cisplatin will not be studied); **S**: Stay at the same dose; **D**: De-escalate to a lower dose;

a. Subjects enrolled at Asian sites and non-Asian sites will be assessed separately. If the dose level for one subgroup has been lowered while the other remains at the higher starting dose, then consideration may be made to increase the dose back to the starting dose based on tolerability in the individual subgroup and the overall population across subgroups.

12.8 List of Abbreviations

Abbreviation/Term	Definition
1L	First Line
2L	Second Line
5-FU	5-fluorouracil
AE	Adverse Event
ADA	Anti-Drug Antibodies
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
AP	Alkaline Phosphatase
ASaT	All Subjects as Treated
aPTT	Activated Partial Thromboplastin Time
ASCO	American Society of Clinical Oncology
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
BICR	Blinded Independent Central Review
BID	Twice a Day
ß-HCG	Beta Human Chorionic Gonadotropin
BSA	Body Surface Area
CBC	Complete Blood Count
CI	Confidence Interval
CNS	Central Nervous System
CPS	Combined Positive Score
CR	Complete Response
CrCl	Calculated Creatinine Clearance
CRF	Case Report Form
CSR	Clinical Study Report
CT	Computed Tomography
CTCAE	Common Toxicity Criteria for Adverse Events
CTLA-4	Cytotoxic T-Lymphocyte-Associated Antigen-4
CTU	Computed Tomography Urography
DCR	Disease Control Rate
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
DOR	Duration of Response
DR	Drug Related
ECI	Events of Clinical Interest
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eDMC	external Data Monitoring Committee
EOC	Executive Oversight Committee
EORTC	European Organization for Research and Treatment of Cancer
ePRO	Electronic Patient Reported Outcomes
ERC	Ethics Review Committee
FA	Final Analysis
FBR	Future Biomedical Research
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FDAMA	Food and Drug Administration Modernization Act
FFPE	Formalin-Fixed, Paraffin-Embedded
FNA	Fine Needle Aspirate

Abbreviation/Term	Definition
FP	Cisplatin + 5-fluoruracil
GCP	Good Clinical Practice
GEJ	Gastroesophageal Junction
5-FU	5-fluoruracil
GFR	Glomerular Filtration Rate
HBsAg	Hepatitis B surface Antigen
HCV	Hepatitis C Virus
HER2/neu	Human Epidermal Growth Factor Receptor 2
HIV	Human Immunodeficiency Virus
HNSCC	Head and Neck Squamous Cell Carcinoma
HPV	Human Papillomavirus
HRQoL	Health Related Quality of Life
IA	Interim Analysis
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IHC	Immunohistochemistry
INR	International Normalized Ratio
irAEs	Immune-related Adverse Events
irRECIST	Modification of RECIST 1.1
IRB	Institutional Review Board
ITIM	Immunoreceptor Tyrosine-based Inhibition Motif
ITSM	Immunoreceptor Tyrosine-based Switch Motif
ITT	Intention To Treat
IV	Intravenous
IVRS	Interactive Voice Response System
IWRS	Integrated Web Response System
Kg	Kilogram
KN	KEYNOTE
LDH	Lactate Dehydrogenase
mAb	Monoclonal Antibody
mcL	Microliters
MEL	Melanoma
Mg	Milligram
Mg/kg	Milligram per Kilogram
mL	milliliter
MRI	Magnetic Resonance Imaging
MSD	Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
MTD	Maximum Tolerated Dose
NA or N/A	Not Applicable
NCI	National Cancer Institute
NSAID	Non-Steroidal Anti-inflammatory Drug
NSCLC	Non-Small Cell Lung Cancer
ORR	Overall Response Rate
OS	Overall Survival
OTC	Over-the-counter
PD	Progressive Disease
PD-1	Programmed Death-1
PD-L1	Programmed Death-Ligand 1
PFS	Progression Free Survival

Abbreviation/Term	Definition
PGt	Pharmacogenetic
PIN	Personal Identification Number
PK	Pharmacokinetic
PK/PD	Pharmacokinetic/Pharmacodynamic
PO	Oral Administration
PR	Partial Response
PRO	Patient Reported Outcomes
PT	Prothrombin Time
PS	Performance Status
QoL	Quality of Life
R/M	Recurrent or Metastatic
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic Acid
RR	Response Rate
QoL	Quality of Life
Q2W	Every 2 Weeks
Q3W	Every 3 Weeks
SAC	Scientific Advisory Committee
SAE	Serious Adverse Events
SAP	Statistical Analysis Plan
SD	Stable disease
SFU	Survival Follow-Up
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
siDMC	Standing Internal Data Monitoring Committee
SIM	Site Imaging Manual
SOC	Standard of Care
SOP	Standard Operating Procedures
T1DM	Type 1 Diabetes Mellitus
TIL	Tumor Infiltrating Lymphocytes
TSH	Thyroid Stimulating Hormone
ULN	Upper Limit of Normal
WBC	White Blood Cell

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 – 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	