Official Protocol Title:	A Phase III, Randomized, Open-label Clinical Trial of Pembrolizumab (MK-3475) versus Paclitaxel in Asian Subjects with Advanced Gastric or Gastroesophageal Junction Adenocarcinoma who Progressed after First-Line Therapy with Platinum and Fluoropyrimidine
NCT number:	NCT03019588
Document Date:	22-Apr-2020

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

TITLE:

A Phase III, Randomized, Open-label Clinical Trial of Pembrolizumab (MK-3475) versus Paclitaxel in Asian Subjects with Advanced Gastric or Gastroesophageal Junction Adenocarcinoma who Progressed after First-Line Therapy with Platinum and Fluoropyrimidine

EudraCT NUMBER: [Not Applicable]

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DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
3475-063-03	22-APR-2020	Added standard extension study language
3475-063-02	17-NOV-2017	Changes made to update dose modification and toxicity management guidelines for pembrolizumab to align with the USPI and SMPC; additional changes made to allow flexibility in the entire follow-up period
3475-063-01	29-MAR-2017	Changes made to exclusion criteria and trial flow chart to be consistent with other pembrolizumab China/Asia pacific studies (except HCC)
3475-063-00	07-JUN-2016	Original protocol

SUMMARY OF CHANGES

PRIMARY REASON(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
1.0	Trial Summary/Duration of Participation	Added: Once the participant has achieved the study objective or the study has ended, the participant is discontinued from the study and may be enrolled in an extension study to continue protocol-defined assessments and treatment.	To include extension study
2.2	Trial Diagram	Added: Study Completion and Pembrolizumab Extension Study	
5.10	Beginning and End of the Trial	Added: Upon study completion, participants are discontinued and may be enrolled in a pembrolizumab extension study. Enrollment in the extension study is conditional on subject consent.	

ADDITIONAL CHANGE(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
1.0	Trial Summary: Duration of Participation	Replaced word "withdraw" with "discontinue": Treatment with pembrolizumab or paclitaxel will continue until documented disease progression, unacceptable adverse event(s), intercurrent illness that prevents further administration of treatment, investigator's decision to ~~withdraw~~ **discontinue** the subject, subject withdraws consent, pregnancy of the subject, subject receives 35 administrations (approximately 2 years) of pembrolizumab, or administrative reasons requiring cessation of treatment.	To align with current pembrolizumab program
1.0 2.1 5.8.1	Trial Summary: Duration of Participation Trial Design Discontinuation of Treatment	Removed: Noncompliance with study treatment or procedure requirements	To align with current pembrolizumab program. The current wording of noncompliance with study treatment or procedure requirements created a protocol deviation when a participant remains on study
4.2.3.5	Future Biomedical Research	Statement updated to: The details of ~~this~~ Future Biomedical Research ~~sub-trial~~ are presented in Section 12.2.	Due to EU CTR changes that will require FBR results to be reported if FBR is indicated as a sub-study to the clinical protocol.

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
5.5.2	Prohibited Concomitant Medication	Systemic glucocorticoids for any purpose other than to modulate symptoms from an ~~event of clinical interest~~ **AE that is suspected to have** an immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor (e.g., for control of acute asthma symptoms).	Event of clinical interest changed to AE since AEs with immunologic etiology are no longer routinely collected as ECIS
6.3	Second Course Phase (Retreatment with Pembrolizumab)	Footnote n: Added "See Section 7.1.2.6.3."	To clarify tumor imaging procedures during Second Course Phase
7.1.1.1.2	Consent and Collection of Specimen for Future Biomedical Research	Statement updated to: The investigator or qualified designee will explain the Future Biomedical Research consent to the participant, 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 participant.	Due to EU CTR changes that will require FBR results to be reported if FBR is indicated as a sub-study to the clinical protocol.
7.1.1.8	Trial Compliance (Medication/Diet/Activity/Other)	Changed the word "witnessed" to "monitored"	To appropriately describe the work being done by the investigator and/or trial staff.
7.1.2.6.3 (Added)	Second Course (Retreatment) Tumor Imaging	Added Section and text describing Second Course Tumor imaging including timing and activities	To clarify tumor imaging procedures during Second Course Phase.

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
7.1.2.6.4	RECIST 1.1 Assessment of Disease	Originally Section 7.1.2.6.3 but moved to 7.1.2.6.4. Therefore, all references to RECIST 1.1 Assessment of Disease were updated to 7.1.2.6.4.	Due to the addition of Second Course (Retreatment) Tumor Imaging (Section 7.1.2.6.3), RECIST 1.1 Assessment of Disease was moved to Section 7.1.2.6.4.
7.1.2.6.5	irRECIST Assessment of Disease	Originally Section 7.1.2.6.4 but moved to 7.1.2.6.5. Therefore, all reference to irRECIST Assessment of Disease were updated to 7.1.2.6.5	Due to the addition of Second Course (Retreatment) Tumor Imaging (Section 7.1.2.6.3), irRECIST Assessment of Disease was moved to Section 7.1.2.6.5.
7.1.5.4.1	Safety Follow-up	Removal of "All AEs that occur prior to the 30-Day Safety Follow-up Visit should be recorded. Subjects with an AE of Grade > 1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new anti-cancer therapy, whichever occurs first. SAEs will be collected for 90 days after the end of the treatment of 30 days following last dose of trial treatment if the subject initiates new anti-cancer therapy, whichever occurs first."	To align with current pembrolizumab program. Original wording introduced conflict for reporting AEs.

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
12.2	Collection and Management of Specimens for Future Biomedical Research	Updated content under: 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~~.	Due to EU CTR changes that will require FBR results to be reported if FBR is indicated as a sub-study to the clinical protocol.
12.2	Collection and Management of Specimens for Future Biomedical Research	Updated content under 5. Biorepository Specimen Usage Any contracted third-party analyses will conform to the specific scope of analysis outlined in **future biomedical research protocol and consent** ~~this sub-trial~~. Future Biomedical Research specimens remaining with the third party after the specific analysis is performed will be reported to the Sponsor.	Due to EU CTR changes that will require FBR results to be reported if FBR is indicated as a sub-study to the clinical protocol.
Throughout	Throughout	Miscellaneous formatting and edits have been corrected	

1.0 TRIAL SUMMARY

Abbreviated Title	Pembrolizumab (MK-3475) vs Paclitaxel in 2L Asian Subjects with Advanced Gastric Adenocarcinoma
Sponsor Product Identifiers	MK-3475 Pembrolizumab
Trial Phase	III
Clinical Indication	Advanced Gastric or Gastroesophageal Junction (GEJ) Adenocarcinoma
Trial Type	Interventional
Type of control	Active control without placebo
Route of administration	Intravenous
Trial Blinding	Unblinded Open-label
Treatment Groups	Arm 1: Pembrolizumab (MK-3475) 200 mg every 3 weeks (Q3W) Arm 2: Paclitaxel 80 mg/m^2 on Days 1, 8, and 15 of every 28 day (4-week) cycle
Number of trial subjects	Approximately 360 subjects will be enrolled.
Estimated duration of trial	The Sponsor estimates that the trial will require approximately 36 months from the time the first subject signs the informed consent until the last subject's last study-related phone call or visit.
Duration of Participation	Each subject will participate in the trial from the time the subject signs the Informed Consent Form (ICF) through the final contact. After a screening phase of up to 28 days, eligible subjects will receive treatment beginning on Day 1 of each 3-week dosing cycle for pembrolizumab or 3 weeks on, 1-week off dosing cycle for paclitaxel. Treatment with pembrolizumab or paclitaxel will continue until documented disease progression, unacceptable adverse event(s), intercurrent illness that prevents further administration of treatment, investigator's decision to discontinue the subject, subject withdraws consent, pregnancy of the subject, subject receives 35 administrations (approximately 2 years) of pembrolizumab, or administrative reasons requiring cessation of treatment. After the end of treatment, each subject will be followed for 30 days for adverse event and events of clinical interest monitoring (serious adverse events 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 within the pembrolizumab arm who discontinue after 35 administrations (approximately 2 years) of therapy for reasons other than disease progression or intolerability or who discontinue after attaining a CR may be eligible for up to one year of retreatment after they have experienced radiographic disease progression. Subjects who discontinue for reasons other than disease progression 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. All subjects will be followed by telephone for overall survival until death, withdrawal of consent, or the end of the study.

	Once the participant has achieved the study objective or the study has ended, the participant is discontinued from the study and may be enrolled in an extension study to continue protocol-defined assessments and treatment.

Randomization Ratio	1:1

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

2.0 TRIAL DESIGN

2.1 Trial Design

This is a randomized, multi-center, open-label trial of pembrolizumab (MK-3475) versus paclitaxel in Asian, programmed death-ligand 1 (PD-L1) positive subjects with advanced gastric or gastroesophageal junction (GEJ) adenocarcinoma who have progressed after failure of any combination chemotherapy containing a platinum and a fluoropyrimidine agent.

In this trial, approximately 360 subjects (approximately 70%-80% of total population from China) will be randomized to compare the efficacy and safety of pembrolizumab versus paclitaxel. Subjects will be randomized in a 1:1 ratio to receive pembrolizumab or paclitaxel and stratified by time to progression on first line therapy (< 6 months vs. ≥ 6 months) and Eastern Cooperative Oncology Group (ECOG) Performance Scale (0 vs. 1).

Subjects will be required to provide tissue of a tumor lesion to be evaluated at a central laboratory for expression status of PD-L1. Only subjects whose tumors express PD-L1 (are PD-L1+) as determined by the central laboratory facility will be eligible for randomization in this study.

All study subjects will be evaluated every 6 weeks (+/- 7 days) following the date of randomization until progression of disease is documented with radiologic imaging (computed tomography or magnetic resonance imaging).

The primary efficacy endpoints are overall survival (OS) and progression-free survival (PFS). The primary PFS analysis will be based on RECIST 1.1 by blinded central radiologists' review. RECIST 1.1 will also be used by the local site for treatment decisions. However, because of the unique tumor responses typical with pembrolizumab, RECIST 1.1 [1] has been modified as described in Section 7.1.2.6.5 to allow for continued treatment and a repeat confirmatory scan in subjects with initial evidence of progressive disease (PD) by standard RECIST 1.1 (hereafter referred to irRECIST). If a subject has progression of disease by RECIST 1.1, it is recommended that the subject be discontinued from the study treatment unless, in the investigator's opinion, the subject is deriving benefit from treatment. Clinically stable subjects, as defined in Section 7.1.2.6.5, may continue to receive trial therapy at the discretion of the investigator. If a repeat scan confirms progression of disease and the subject remains clinically stable, the subject may continue treatment after consultation with the Sponsor.

Adverse events 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.

Except as noted above, treatment with pembrolizumab or paclitaxel will continue until documented disease progression, unacceptable adverse event(s), intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw the subject, subject withdraws consent, pregnancy of the subject, completion of 35 administrations (approximately 2 years) of pembrolizumab, or administrative reasons requiring the cessation of treatment.

Subjects on the pembrolizumab arm, who attain an investigator-determined confirmed complete response (CR), may consider stopping trial treatment after receiving at least 24 weeks of treatment with pembrolizumab. Subjects who discontinue after 35 administrations (approximately 2 years) of pembrolizumab for reasons other than disease progression or intolerability or who discontinue after attaining a CR may be eligible for up to one year of retreatment after they have experienced radiographic disease progression. The decision to retreat will be at the discretion of the investigator only if no cancer treatment was administered since the last dose of pembrolizumab, the subject still meets the safety parameters listed in the Inclusion/Exclusion criteria and the trial remains open (refer to Section 7.1.5.5 for further details). Subjects within the paclitaxel arm will continue on treatment until disease progression or unacceptable toxicity. A cross-over of treatment groups after documented disease progression on the study treatment will not be allowed.

After the end of treatment, each subject will be followed for 30 days for adverse event and events of clinical interest monitoring (serious adverse events 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 disease progression 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. All subjects will be followed by telephone contact for overall survival until death, withdrawal of consent or the end of the study, whichever comes first.

This study will be conducted in conformance with Good Clinical Practices.

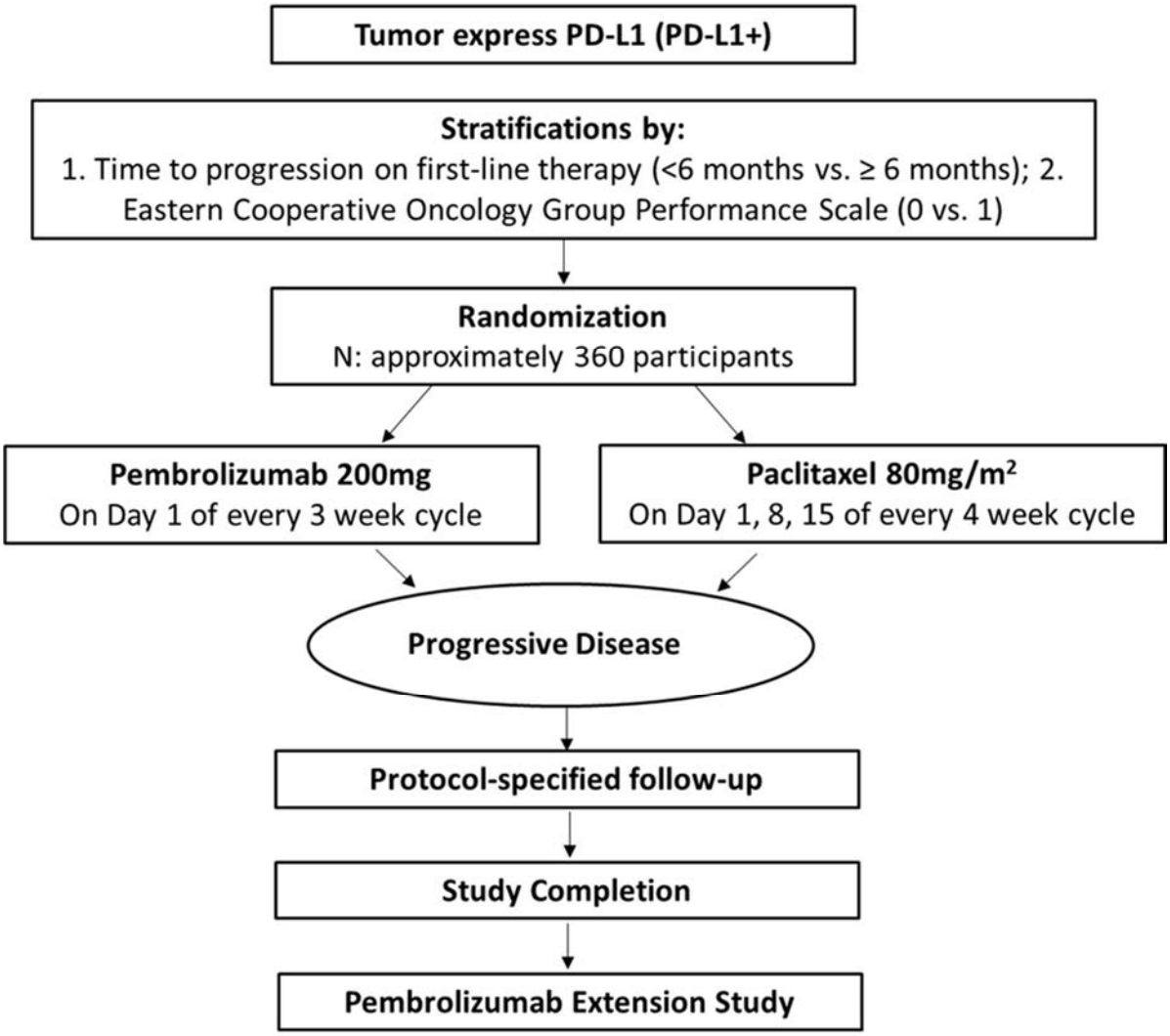
Specific procedures to be performed during the trial, as well as their prescribed times and associated visit windows, are outlined in the Trial Flow Chart - Section 6.0. Details of each procedure are provided in Section 7.0 – Trial Procedures.

This trial will use an independent, external Data Monitoring Committee (eDMC) to monitor safety and efficacy. The role of the eDMC will be clearly elucidated in the eDMC Charter. There will be one formal interim analysis for OS and no interim analysis for PFS. For further details, please refer to Section 8 of the protocol.

2.2 Trial Diagram

The trial design is depicted in Figure 1

Figure 1 Trial Design Schematic



3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

In PD-L1 positive subjects with advanced gastric or GEJ adenocarcinoma who have progressed on one previous line of therapy.

3.1 Primary Objective(s) & Hypothesis(es)

(1) **Objective**: To compare OS.
Hypothesis: Pembrolizumab prolongs OS compared to paclitaxel.

(2) **Objective**: To compare PFS per RECIST 1.1 by blinded central radiologists' review.
Hypotheses: Pembrolizumab prolongs PFS per RECIST 1.1 by blinded central radiologists' review compared to paclitaxel.

The study is considered to have met its primary objective if pembrolizumab is superior to paclitaxel either in OS (interim or final analysis) or in the final PFS analysis.

3.2 Secondary Objective(s) & Hypothesis(es)

(1) To evaluate the Objective Response Rate (ORR) per RECIST 1.1 assessed by blinded central radiologists' review.
Hypotheses: Pembrolizumab improves ORR per RECIST 1.1 assessed by blinded central radiologists' review compared to paclitaxel.

(2) **Objective**: Evaluate the safety and tolerability profile of pembrolizumab compared to paclitaxel.

3.3 Exploratory Objectives

(1) **Objective:** To evaluate PFS per immune-related RECIST (irRECIST) by blinded central radiologists' review among subjects when treated with pembrolizumab compared to paclitaxel.

(2) **Objective:** To evaluate the Time to Progression (TTP) and Duration of Response (DOR) per RECIST 1.1 by blinded central radiologists' review among subjects when treated with pembrolizumab compared to paclitaxel.

(3) **Objective**: To evaluate score change of health related quality of Life using the EORTC QLQ-C30 and the EORTC QLQ-STO22 from baseline among subjects when treated with pembrolizumab compared to paclitaxel.

(4) **Objective**: To characterize utilities using EuroQol EQ-5D among subjects when treated with pembrolizumab compared to paclitaxel.

(5) **Objective**: To explore the relationship between genetic variation and response to the treatment(s) administered. Genomic variability will be analyzed for association with clinical data collected in this study.

4.0 BACKGROUND & RATIONALE

4.1 Background

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

4.1.1 Pharmaceutical and Therapeutic Background

4.1.1.1 Gastric cancer Worldwide and in Asia/China

Gastric cancer is the fifth most commonly diagnosed cancer and the third most common cause of cancer-related deaths worldwide [2]. In China, gastric cancer is one of the most common malignancies, ranking second in incidence and third in mortality [3]. In 2012, there were approximately 952,000 new cases (half the world total occurs in Eastern Asia) of gastric cancer and 723,000 deaths worldwide; of these, approximately 405,000 new cases (43%) and 325,000 deaths (45%) occurred in China [3].

To date, surgery is still the only curative treatment for patients with gastric cancer, but this is only an option for patients with early or locally advanced gastric cancer. At present, the early-stage diagnosis rate is low in China, and as a result, most patients have advanced or metastatic gastric cancer at diagnosis; as reported by Chinese Society of Clinical Oncology (CSCO), 31.2% and 39.8% were stage IV and stage III at diagnosis (CSCO gastric cancer survey, 2011). The only treatment option for patients with advanced gastric cancer is chemotherapy, although the efficacy of such treatment is limited [4-6]. Many patients initially respond to chemotherapy, but treatment is not curative, and patients experience progression. Second-line once-per-week paclitaxel is widely used in this setting in Asian countries, with median OS of 151 days to 9.5 months and PFS of 2.6 to 3.6 months [7-9].

4.1.1.2 Anti-PD-1 Blockage for Malignancy

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades [10]. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies [11-15]. In particular, the presence of cluster of differentiation (CD)8+ 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 tumors.

The programmed cell death 1 (PD-1) receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an Ig superfamily member related to CD28 and cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) that has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or programmed death-ligand 2 [PD-L2]) [16, 17]. The structure of murine PD-1 has been resolved [18]. 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 signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling 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 signaling cascade [16, 19-21]. The mechanism by which PD-1

down modulates T-cell responses is similar to, but distinct from that of CTLA-4 as both molecules regulate an overlapping set of signaling proteins [22, 23]. 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 [24, 25]. Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells [26]. The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types, including non-hematopoietic tissues as well as in various tumors [22, 27-29]. Both ligands are type I transmembrane receptors containing both IgV- and IgC-like domains in the extracellular region and contain short cytoplasmic regions with no known signaling motifs. Binding of either 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 [22]. 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 tumor-specific T-cell expansion in patients with melanoma [30].

In gastric cancer PD-L1 and PD-L2 overexpression have recently been associated with EBV-positive tumors [31]. This suggests that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention.

4.1.1.3 Anti PD-1 Antibody, Pembrolizumab

Pembrolizumab (MK-3475) is a potent and highly selective humanized monoclonal antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Keytruda® (pembrolizumab) has recently been approved in the United States for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilumumab and, if BRAF V600 mutation positive, a BRAF inhibitor.

4.1.2 Pre-clinical Studies of Pembrolizumab

Therapeutic studies in mouse models have shown that administration of antibodies blocking PD-1/PD-L1 interaction enhances infiltration of tumor-specific CD8+ T-cells and leads ultimately to tumor rejection, either as a mono-therapy or in combination with other treatment modalities. Anti-mouse PD-1 or anti-mouse PD-L1 antibodies have demonstrated anti-tumor 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 tumor 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 [32-37]. 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 tumor models (see the IB).

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

4.1.3 Ongoing Clinical Trials

Ongoing clinical trials are being conducted in advanced melanoma, NSCLC, a number of advanced solid tumor 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 012 (KN012) [38]. Thirty-nine subjects (19 from clinical trial sites in Asia and 20 from trial sites outside Asia) who had metastatic gastric or GEJ adenocarcinoma, ECOG performance status of 0 or 1, and tumor positive for PD-L1 by immunohistochemistry (defined as staining in ≥1% of tumor cells or any stroma cells using a prototype assay) received single agent pembrolizumab at a dose of 10 mg/kg every 2 weeks. The number of prior systemic treatments for metastatic disease ranged from zero to greater than 4. The primary efficacy endpoint was overall response rate (ORR). Overall, the interim ORR is 30.8% (95% confidence interval [CI] [17.0%, 47.6%]; all partial responses), while the interim disease control rate (DCR) is 43.6% (95% CI [27.8%, 60.4%]). 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. It should be noted that in the non-Asia group, subjects had less prior therapy relative to the Asian subjects, and that ORR in later line subjects (≥3L) was higher in the Asian group (1 partial response [PR]/7 subjects in the non-Asia group, 4 PR/13 subjects in the Asia group). As of the data cutoff (06 Aug 2014), the overall median duration of follow-up is 6-months, and 11/12 subjects who responded are still continuing. 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 every 2 weeks was generally well tolerated, with the type, severity, and frequency of adverse events similar to that observed in other indications (see the IB for information about adverse events in other indications). There was 1 death reported in the gastric cancer cohort. This was a subject who had adverse events of tracheomalacia (Grade 3) and hypoxia (Grade 5). The investigator considered the Grade 5 hypoxia related to the study treatment.

KN059 is a non-randomized, multi-site, open-label trial of pembrolizumab in subjects with gastric or gastroesophageal junction adenocarcinoma. Approximately 223 subjects may be enrolled across three cohorts to examine the safety and efficacy of pembrolizumab: Cohort 1) subjects who have progressed on at least 2 prior systemic treatments for advanced disease (3L+ subjects) that will receive pembrolizumab as monotherapy; Cohort 2) subjects who have not previously received systemic therapy for advanced disease (1L subjects) who will receive pembrolizumab in combination with cisplatin and 5-FU. Sites in Japan will also administer pembrolizumab in combination with cisplatin and capecitabine; and Cohort 3) PD-L1 positive subjects who have not previously received systemic therapy for advanced

disease (1L subjects) who will receive pembrolizumab as monotherapy. The primary objectives of the trial are to determine the safety, tolerability, and ORR of pembrolizumab (200 mg fixed dose every 3 weeks [Q3W]) given as first and third line monotherapy to subjects with gastric or gastroesophageal junction adenocarcinoma whose tumors express PD-L1, and to determine the safety and tolerability of pembrolizumab administered in combination with cisplatin and 5-FU as first line therapy in subjects with gastric or gastroesophageal junction adenocarcinoma.

KN061 is a randomized, multi-center, open-label trial of pembrolizumab versus paclitaxel in subjects with advanced gastric or gastroesophageal junction adenocarcinoma who have progressed after failure of any combination chemotherapy containing a platinum and a fluoropyrimidine agent. Up to 720 subjects will be randomized; the enrollment will include all subjects without regard for PD-L1 expression status. The overall study enrollment will be driven by the number of subjects with PD-L1 positive expression on their tumor (n = 360). That is, enrollment will stop when approximately 360 subjects with PD-L1 positive expression on their tumor have been randomized. Additionally, there will be a cap on enrollment (30% of total) for subjects residing in the Asia Pacific region for this study. The primary efficacy endpoints are PFS and overall survival (OS). The primary PFS analysis will be based on RECIST 1.1 by blinded central radiologists' review. RECIST 1.1 will also be used by the local site for treatment decisions.

KN062 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 PD-L1 positive, 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. Subjects will be randomized in a 1:1:1 ratio among the three treatment arms, stratified by geographic region, disease status, and fluoropyrimidine treatment. There will be one interim PFS/OS analysis, one planned interim safety analysis, and quarterly safety monitoring.

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

Trials evaluating pembrolizumab in gastric cancer have demonstrated clinical activity in subjects with 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). This study is designed to investigate if pembrolizumab monotherapy in second line gastric cancer subjects improves OS and PFS.

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

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

Among the 8 randomized dose-comparison studies, a total of 2262 subjects were enrolled with melanoma and NSCLC, covering different disease settings (treatment naïve, previously treated, PD-L1 enriched and all-comers) and different treatment settings (monotherapy and in combination with chemotherapy). Five studies compared 2 mg/kg Q3W vs. 10 mg/kg Q3W (KN001 B2, KN001 D, KN002, KN010, and KN021), and 3 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 dose provided similar responses to the highest doses studied. Subsequently, flat dose-/exposure-response relationships were also observed in other tumor types, including head and neck cancer, bladder cancer, gastric cancer, and classical Hodgkin's Lymphoma, confirming 200 mg Q3W as the appropriate dose independent of the tumor type. These findings are consistent with the mechanism of action of pembrolizumab, which acts by interaction with immune cells, and not via direct binding to cancer cells.

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

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

4.2.2.1 Rationale for Paclitaxel as the Comparator

The use of paclitaxel at a dose of 80 mg/m^2 intravenously administered on Days 1, 8, and 15 of a 28-day (4 week) cycle has become a common practice in the second-line treatment of metastatic gastric cancer globally and this regimen was used as a chemotherapy backbone and control in the RAINBOW study and the TyTAN study [39, 40].

Ramucirumab, an anti-vascular endothelial growth factor receptor 2 antibody (VEGFR2), was approved by the US FDA as monotherapy for second line gastric cancer in April 2014, based on the results from the REGARD study [41]. The REGARD study was a Phase 3 study comparing ramucirumab monotherapy (8 mg/kg intravenous infusion on days 1 and 15 every 4 weeks), versus best supportive care (BSC) in subjects refractory to previous fluoropyrimidine treatment (with or without platinum). Ramucirumab significantly improved OS (5.2 mo vs 3.8 mo with BSC, HR = 0.776, P = 0.047) and PFS (2.1 mo vs 1.3 mo with BSC, HR 0.483, P < 0.0001)

The combination of ramucirumab plus paclitaxel was approved for second line gastric cancer by the US FDA in November, 2014, based on results from the RAINBOW study [39]. RAINBOW was a Phase 3 study testing paclitaxel (80 mg/m^2 on days 1, 8, and 15, of a 28 day cycle) with or without ramucirumab (8 mg/kg intra-venous infusion on days 1 and 15 of a 28 day cycle) in subjects with metastatic gastric cancer refractory or progressive after first-line therapy with a platinum and a fluoropyrimidine. Median overall survival was 9.6 months for the combination and 7.4 months for paclitaxel alone with a HR 0.807(P = 0.0169) favoring the group receiving ramucirumab. Median progression-free survival was 4.4 months and 2.9 months, respectively, with a HR of 0.635 (P < 0.0001). Adverse events of grade ≥ 3 were somewhat greater with combination treatment and included neutropenia (40.7% vs 18.8%), leukopenia (17.4% vs 6.7%), hypertension (14.1% vs 2.4%) and fatigue (7.0% vs 4.0%).

Although ramucirumab was approved as monotherapy and combination with paclitaxel in the US, ramucirumab containing regimens are not considered current standard of care for second line treatment globally; the paclitaxel regimen (given on Days 1, 8, and 15 of a 28 day (4-week) cycle [3-weeks on, 1-week off dosing cycle]) remains a standard therapy for second-line treatment of gastric cancer globally.

4.2.3 Rationale for Endpoints

4.2.3.1 Efficacy Endpoints

This trial will use overall survival (OS) and progression free survival (PFS) as a dual primary endpoint. The endpoint of OS is the standard for demonstrating superiority of antineoplastic therapy in clinical studies in the area of oncology. Additionally, 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 progression, as this methodology is uniformly 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 assessment of progression.

RECIST 1.1 will also be used by the local site for treatment decisions for both arms of the study. However RECIST 1.1 will be adapted to account for the unique tumor response profile seen with immunotherapies such as pembrolizumab. Immunotherapeutic agents such as pembrolizumab may produce antitumor effects by potentiating endogenous cancer-specific immune responses which may be functionally anergic. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents, and can manifest a clinical response after an initial increase in tumor burden or even the appearance of new lesions. Standard RECIST criteria may not provide a complete response assessment of immunotherapeutic agents such as pembrolizumab. Therefore, RECIST 1.1 will be used with the following adaptation, outlined in Section 7.1.2.6.5, termed irRECIST.

When feasible, subjects within the pembrolizumab arm should not be discontinued until progression is confirmed. This allowance to continue treatment despite initial radiologic progression takes into account the observation that some subjects can have a transient tumor flare in the first few months after the start of immunotherapy, but with subsequent disease response.

4.2.3.2 Secondary Efficacy Endpoints

The secondary efficacy endpoint of this study is ORR per RECIST 1.1 assessed by blinded central radiologists' review.

4.2.3.3 Safety Endpoints

The primary safety objective of this trial is to characterize the safety and tolerability of pembrolizumab in subjects with metastatic gastric cancer. The primary 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 pembrolizumab compared to paclitaxel including serious adverse events (SAEs) and events of clinical interest (ECIs).

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. Adverse Events (AEs) will be analyzed including but not limited to all AEs, SAEs, fatal AEs, and laboratory changes.

4.2.3.4 Exploratory Endpoints

4.2.3.4.1 Exploratory Efficacy Endpoints

The exploratory endpoints of this study includes efficacy endpoints to evaluate PFS per irRECIST by blinded central radiologists' review, and the Time to Progression (TTP) and Duration of Response (DOR) per RECIST 1.1 by blinded central radiologists' review among subjects when treated with pembrolizumab compared to paclitaxel.

4.2.3.4.2 Patient Reported Outcomes

As part of the exploratory analyses, subjects will provide information regarding their health-related quality of life (HRQoL) via the following assessment tools: EORTC QLQ-C30 and QLQ-STO22, and EuroQol-5D (EQ-5D) questionnaires. These measures are not pure efficacy or safety endpoints because they are affected by both disease progression and treatment tolerability.

EORTC QLQ-C30 and EORTC QLQ-STO22

The EORTC-QLQC30 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, diarrhea, and financial impact), and a global health and quality of life scale [42]. 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 study Flow Chart, beginning with Cycle 1 until 30 days post-treatment discontinuation.

EuroQoL-5D

The EuroQol-5D (EQ-5D) is a standardized instrument for use as a measure of health outcome. The EQ-5D 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 [43]. Each dimension is rated on a three point scale from 1 (extreme problem) to 3 (no problem). The EQ-5D 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 EQ-5D 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 study Flow Chart, beginning with Cycle 1 until 30 days post-treatment discontinuation.

4.2.3.4.3 Exploratory Biomarkers

Introduction: Cancer immunotherapies represent an important and novel class of anti-tumor agents. However, the mechanism of action of these exciting new therapies is not completely understood and much remains to be learned regarding how best to leverage these new drugs in treating patients. Thus, to aid future patients, it is important to investigate the determinants of response or resistance to cancer immunotherapy as well as determinants of adverse events in the course of our clinical trials. These efforts will identify novel predictive/pharmacodynamic biomarkers and generate information that will better guide single-agent and combination therapy with immuno-oncology drugs. To identify novel biomarkers, we will collect biospecimens (blood components, tumor material, etc.) to support analyses of cellular components (e.g., protein, DNA, RNA, metabolites) and other circulating molecules. Investigations may include but are not limited to:

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

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

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

Proteomics and immunohistochemistry (IHC) using blood or tumor: Tumor and blood samples from this study may undergo proteomic analyses (e.g., PD-L1 IHC). PD-L1 protein

level in tumor sections, assessed by IHC, has been shown to correlate with response to pembrolizumab in patients with NSCLC, and an IVD device has been developed for use with pembrolizumab in NSCLC. Preliminary data indicate that this association may also be true in additional cancer types (i.e., triple-negative breast cancer, head and neck, and gastric). Additional tumor or blood-derived proteins may also correlate with response to pembrolizumab. Therefore, tumor tissue may be subjected to proteomic analyses using a variety of platforms that could include but are not limited to immunoassays, liquid chromatography/mass spectrometry. This approach could identify novel protein biomarkers that could aid in patient selection for pembrolizumab (MK-3475) therapy.

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

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

4.2.3.5 Future Biomedical Research

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

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

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

Male/Female Asian subjects with advanced 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 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 histologically or cytologically confirmed diagnosis of gastric or GEJ adenocarcinoma.
4. Have metastatic disease or locally advanced, unresectable disease.
5. Have measurable disease as defined by RECIST 1.1 as determined by investigator. 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.
6. 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 study therapy.
7. Has experienced documented objective radiographic or clinical disease progression during or after first-line therapy containing any platinum/fluoropyrimidine doublet.
    a. To be considered as second-line, the subject needs to have the documentation of disease progression on first-line treatment. The disease progression can be confirmed by CT scan or by clinical evidence (such as cytology report from newly developed ascites and plural effusion).
    b. Any new or worsening malignant effusion (documented by ultrasound) may be confirmed by pathologic criteria (histology and/or cytology) if appropriate.
    c. A subject experiencing clinical disease progression during or within 6 months following the last dose of adjuvant or neo-adjuvant therapy will be eligible for enrollment provided they received a platinum/fluoropyrimidine doublet as required.

d. To be eligible, the subject is required to have received at least one dose of platinum and fluoropyrimidine therapy. The dose reduction and discontinuation of one of these drugs, switching to/adding new drugs on the first-line treatment is allowed; however, the documentation of disease progression on/after the first-line treatment is required. Therefore, subjects with discontinuation due to adverse events on first-line treatment prior to disease progression are not eligible until disease progression is confirmed by documentation.

8. Be willing to provide tissue for PD-L1 biomarker analysis and, based on the adequacy of the tissue sample quality for assessment of PD-L1 status, receives notification of adequate sample from the core lab. Repeat samples may be required if adequate tissue is not provided. Newly obtained biopsy specimens are preferred to archived samples and formalin-fixed, paraffin-embedded (FFPE) block specimens are preferred to slides.

   a. Newly obtained is defined as a specimen obtained up to 6 weeks (42 days) prior to initiation of treatment on Day 1. Subjects for whom newly obtained endoscopic samples cannot be provided (e.g., inaccessible or subject safety concern) may submit an archived specimen.

9. Have tumor express PD-L1 positive (based on analysis of sample provided to core lab).

10. Subjects with HER-2/neu negative tumors are eligible. For subjects with HER2/neu positive tumors or have an unknown tumor status, need to match the following:

    a. If HER2/neu positive, subject must have documentation of disease progression on treatment containing trastuzumab.

    b. Subjects with unknown status must have their HER2/neu status determined locally. If HER2/neu negative, the subject will be eligible. If HER2/neu positive, the subject must have documentation of disease progression on treatment containing trastuzumab.

11. Female subjects of childbearing potential should be willing to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study treatment for the pembrolizumab arm and through 180 days after the last dose of study treatment for the paclitaxel arm (Section 5.7.2). Subjects of childbearing potential are those who have not been surgically sterilized or have not been free from menses for > 1 year.

    Male subjects should agree to use an adequate method of contraception starting with the first dose of study therapy through 120 days after the last dose of study treatment for the pembrolizumab arm and through 180 days after the last dose of study treatment for the paclitaxel arm.

12. Demonstrate adequate organ function as defined in Table 1. All screening labs should be performed within 10 days of trail treatment initiation.

Table 1 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1,500 /mcL
Platelets	≥100,000 / mcL
Hemoglobin	≥9 g/dL or ≥5.6 mmol/L without transfusion or EPO dependency within 7 days.
Renal	
Creatinine **OR** Measured or calculated 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 *Note: Creatinine clearance should be calculated per institutional standard*
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

13. Female subjects of childbearing potential should have a negative urine or serum pregnancy test within 72 hours prior to receiving the first dose of study therapy. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

5.1.3 Subject Exclusion Criteria

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

1. Is currently participating and receiving study therapy or has participated in a study of an investigational agent and received study therapy or used an investigation device within 4 weeks of the first dose of treatment.
2. Has squamous cell or undifferentiated gastric cancer.
3. Has active autoimmune disease that has required systemic treatment in past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement

therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.

4. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.

5. Has had a prior anti-cancer monoclonal antibody (mAb) within 4 weeks prior to the first dose of trial treatment or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to agents administered more than 4 weeks earlier.

6. Has had prior chemotherapy, targeted small molecule therapy, radiation therapy, or any other agents used as systemic treatment for cancer, within 2 weeks prior to the first dose of trial treatment or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to a previously administered agent. *Note: Subjects with ≤ Grade 2 neuropathy or ≤ Grade 2 alopecia are an exception to this criterion and may qualify for the study.*

   a. *If subject received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.*

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

   Note: Subjects with basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or carcinoma in situ (e.g. breast carcinoma, cervical cancer in situ) that have undergone potentially curative therapy are not excluded.

8. Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are radiologically stable, i.e. without evidence of progression for at least 4 weeks by repeat imaging (note that the repeat imaging should be performed during study screening), clinically stable and without requirement of steroid treatment for at least 14 days prior to first dose of trial treatment.

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, 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 study treatment for the pembrolizumab arm and through 180 days after the last dose of study treatment for the paclitaxel arm.

14. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent or with an agent directed to another stimulatory or co-inhibitory T-cell receptor (e.g., CTLA-4, OX-40, CD137).
15. Has a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).
16. Has known active Hepatitis B or C. Active Hepatitis B is defined as a known positive HBsAg result. Active Hepatitis C is defined by a known positive Hepatitis C Ab result or known quantitative HCV RNA results greater than the lower limits of detection of the assay.
17. Has received a live vaccine within 30 days of planned start of study therapy.
    a. *Note: Seasonal influenza vaccines for injection are generally inactivated flu vaccines and are allowed; however intranasal influenza vaccines (e.g., FluMist®) are live attenuated vaccines, and are not allowed.*
18. Known allergy or hypersensitivity to paclitaxel or any components used in the paclitaxel preparation or other contraindication for taxane therapy.

5.2 Trial Treatment(s)

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

Table 2 Trial Treatment

Drug	Dose/ Potency	Dose Frequency	Route of Administration	Regimen/ Treatment Period	Use
Pembrolizumab	200 mg	Every 3 weeks	IV infusion	Day 1 of each 3-week cycle	Experimental
Paclitaxel	80 mg/m^2	3 weeks on, 1 week off	IV infusion	Days 1, 8, and 15 of each 28-day (4-week) cycle	Comparator Regimen

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

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

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

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

5.2.1 Dose Selection/Modification

5.2.1.1 Dose Selection (Preparation)

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

Preparation and administration of paclitaxel should be completed as per the approved product label. Body surface area (BSA) in m^2 should be calculated per local guidance.

5.2.1.2 Dose Modification (Escalation/Titration/Other)

5.2.1.2.1 Dose Modification and Toxicity Management Guidelines for Pembrolizumab

Dose modification and toxicity management for immune-related AEs associated with pembrolizumab

Adverse events associated with pembrolizumab exposure may represent an immunologic etiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical trial data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids, and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, or skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab and administer corticosteroids. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab are provided in Table 3.

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

Immune-related AEs	Toxicity grade or conditions (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 Hyperglycemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold	• Initiate insulin replacement therapy for participants with T1DM • Administer anti-hyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes.
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (e.g., 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 (e.g., 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 etiology 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 etiology 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: GBS (Guillain-Barre Syndrome), SOTR (solid organ transplant rejection), 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 participants 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 4.

Table 4 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 (e.g., 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 (e.g., 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 pembrolizumab (MK-3475) with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of analgesic).

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: Epinephrine** IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Oxygen Pressors Corticosteroids Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. **Subject is permanently discontinued from further study drug treatment.**	No subsequent dosing
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 patient's study record.

5.2.1.2.2 Dose Modification for Paclitaxel

Prior to each administration of study therapy, hematology and liver function must be adequate (see Table 5), and all toxicities must have resolved to Grade < 2 or baseline. Otherwise, hold study treatment until resolution. Pre-infusion laboratory data may not be older than 48 hours.

The paclitaxel dose will be reduced by 10 mg/m^2 when NCI-CTCAE (Version 4.0) Grade 4 hematological toxicity or Grade 3 paclitaxel-related non-hematological toxicity is observed. If the dose of paclitaxel is reduced because of potentially related AEs, subsequent dose increases are not permitted. Paclitaxel will be permanently discontinued if dose reduction to less than 60 mg/m^2 would be required, or in case of any paclitaxel-related event that is deemed life-threatening, regardless of grade. Any proposed variations to the dosing

medication guidelines may be approved after being discussed with a medically qualified Sponsor representative.

Table 5 Criteria for Paclitaxel Treatment on Each Cycle

Parameter	**Criterion**
Absolute neutrophil count	$\geq 1.0 \times 10^9$/L
Platelet count	$\geq 75 \times 10^9$/L
Bilirubin	$\leq 1.5 \times$ ULN
AST/ALT	$\leq 3 \times$ ULN, or $< 5 \times$ ULN if the aminotransferase elevation is due to liver metastases
Paclitaxel-related toxicities/AEs	NCI-CTCAE Version 4.00 Grade < 2 or baseline (except for alopecia)

In each case of hypersensitivity reaction associated with paclitaxel (see Table 6), the investigator should institute treatment measures according to the best available medical practice.

Table 6 Guidelines for Hypersensitivity Reactions in Paclitaxel Arm

Severity	**Action Taken with Paclitaxel at onset of AE**	**Supportive Care**	**Discontinue Paclitaxel**
Grade 1	No Action	Supervise at bedside	NA
Grade 2	Stop Infusion	Administer diphenhydramine 25 to 50 mg I.V. and dexamethasone 8-20 mg I.V. (or equivalent, per institutional guidelines). Resume the paclitaxel infusion after recovery of symptoms at a reduced rate (20 mL/hour for 15 minutes). The infusion rate may then be increased to 40 mL/hour for 15 minutes, and subsequently at the full rate if symptoms do not recur	If symptoms recur.
Grade 3/4	Stop Infusion	Give I.V. diphenhydramine and dexamethasone (per institutional guidelines). Add epinephrine or bronchodilators if indicated. The subject should be removed from paclitaxel treatment.	At first occurrence

In addition, investigators may withdraw a subject from paclitaxel therapy for any of the following reasons:

- An unacceptable adverse event/toxicity (e.g., a persistent moderate toxicity that is intolerable to the subject) and is, in the opinion of the investigator, clearly attributed to paclitaxel

- Any event which would warrant paclitaxel therapy to be modified by more than two dose reductions or to be held for more than 4 weeks from the last administered dose, and is clearly attributed to paclitaxel (i.e. recurrent or persistent neuropathy).

Dosing interruptions are permitted in the case of medical/surgical events or logistical reasons not related to study therapy (e.g., elective surgery, unrelated medical events, patient vacation, and/or holidays). Subjects should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the patient's study record.

5.2.2 Timing of Dose Administration

Trial treatment of pembrolizumab may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons (up to 3 days after subject is randomization is permitted). Trial treatment of paclitaxel may be administered up to 3 days after the scheduled dosing visits of each cycle due to administrative reasons. If dosing is delayed due to administrative reasons, the subsequent dosing visit should be re-calculated to account for the weekly dosing visits.

5.2.2.1 Pembrolizumab

Pembrolizumab should be administered on Day 1 of each three week cycle (Q3W) after all procedures/assessments have been completed as detailed on the Trial Flow Chart (Section 6.0). Trial treatment may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons.

Pembrolizumab 200 mg will be administered as a 30 minute IV infusion Q3W. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 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.

5.2.2.2 Paclitaxel

Paclitaxel should be administered on Day 1, 8, and 15 of each four week cycle after all procedures/assessments have been completed as detailed on the Trial Flow Chart (Section 6.0). Paclitaxel should be administered intravenously over approximately 1 hour according to manufacturer standards, at a dose of 80 mg/m^2. The first dose of paclitaxel is dependent upon the subject's baseline body surface area. Subsequent doses of paclitaxel must be recalculated if there is a $\geq$ 10% change (increase or decrease) in body surface area from baseline; subsequent doses may be recalculated if there is a < 10% change (increase or decrease) in body surface area from baseline.

Premedication is recommended prior to infusion of paclitaxel according to the manufacturer's instructions and local standards. Premedication will consist of an oral steroid (such as dexamethasone 8-20 mg or equivalent administered [PO] 12 and 6 hours or [IV]

30-60 minutes before paclitaxel), an antihistamine (H1 antagonist) such as diphenhydramine hydrochloride 50 mg I.V. (or equivalent), cimetidine (H2 antagonist) 300 mg I.V. or equivalent, and an antiemetic (such as ondansetron 8 mg dose PO or 0.15 mg/kg I.V. as per ondansetron prescribing information), administered 30 to 120 minutes before paclitaxel. Premedication may be provided per local guidance and all medications should be captured on the appropriate case report form.

5.2.3 Trial Blinding

This is an open-label trial; therefore, the Sponsor, investigator and subject will know the treatment administered.

Imaging data for the primary analysis will be centrally reviewed by independent radiologist(s) without knowledge of subject treatment assignment.

5.3 Randomization or Treatment Allocation

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

5.4 Stratification

Treatment allocation/randomization will be stratified according to the following factors:

1. Time to progression from the first dose of first-line therapy (< 6 months vs. ≥ 6 months)
2. Eastern Cooperative Oncology Group (ECOG) Performance Status (0 vs. 1)

5.5 Concomitant Medications/Vaccinations (Allowed & Prohibited)

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

5.5.1 Acceptable Concomitant Medications

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

All concomitant medications received within 30 days before the first dose of trial treatment and 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 as defined in Section 7.2.

5.5.2 Prohibited Concomitant Medication

Subjects are prohibited from receiving the following therapies during the Screening and Treatment Phase (including retreatment for post-complete response relapse) of this trial:

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab
- Radiation therapy
  - Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed after consultation with Sponsor.
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, 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 (e.g. *FluMist*®) are not allowed.
- Pembrolizumab arm only: Systemic glucocorticoids for any purpose other than to modulate symptoms from an AE that is suspected to have an immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor (e.g., for control of acute asthma symptoms).

  Note: for urgent medical condition, systemic glucocorticoids can be used before the consultation with the Sponsor; the investigators will subsequently provide detailed documentation for the sponsor regarding the case.

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

The Exclusion Criteria describes other medications which are prohibited in this trial.

There are no prohibited therapies during the Post-Treatment Follow-up Phase; however, participants must be discontinued from the safety follow-up phase if they begin a non-trial treatment.

For those participants randomized to the paclitaxel arm of the study, pre-medication with steroids is acceptable.

5.6 Rescue Medications & Supportive Care

5.6.1 Supportive Care Guidelines for Pembrolizumab

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

Note: If after the evaluation of the event, it is determined not to be related to pembrolizumab, the investigator does not need to follow the treatment guidance. Refer to Table 3 in Section 5.2.1.2.1 for guidelines regarding dose modification and supportive care.

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

5.6.2 Supportive Care Guidelines for Paclitaxel

Palliative and supportive care for other disease-related symptoms and for toxicity associated with treatment will be offered to subjects within the paclitaxel arm of this trial. Supportive care measures may include but are not limited to antidiarrheal agents, antiemetic agents, opiate and nonopiate analgesic agents, appetite stimulants, and granulocyte and erythroid growth factors. Non-drug supportive care procedures may be performed as medically necessary and appropriate in the opinion of the investigator. Details of interventions, procedures, or blood products (e.g., blood cells, platelets, or fresh frozen plasma transfusions) should be recorded on the eCRF. Appropriate management of hypersensitivity reactions is described in Section 5.2.1.2.2 and Table 6. The uses of other specific supportive care agents are presented below.

- Diarrhea:
  - In the event of Grade 3 or 4 diarrhea, supportive measures may include hydration, loperamide, octreotide, and antidiarrheals.
  - If diarrhea is severe (i.e., requires intravenous hydration) and associated with fever or severe (Grade 3 or 4) neutropenia, broad-spectrum antibiotics may be prescribed.
  - Subjects with severe diarrhea or any diarrhea associated with severe nausea or vomiting must be hospitalized for intravenous hydration and correction of electrolyte imbalance.
- Nausea/Vomiting:
  - The use of antiemetic agents is permitted at the discretion of the investigator.

Additional Supportive Care Guidelines:

- Analgesic Agents:

The use of analgesic agents is permitted at the discretion of the investigator. The chronic use of non-steroidal anti-inflammatory drugs (NSAIDs) with a high risk of bleeding (e.g., indomethacin, ibuprofen, naproxen, or similar agents) is strongly discouraged unless at the discretion and responsibility of the investigator after careful assessment of the individual bleeding risk of the subject. Chronic use of analgesic agents with no or low bleeding risk (e.g., paracetamol/acetaminophen, metamizole, dipyrone, propyphenazone) is acceptable.

- Granulocyte-Colony Stimulating Factors:

The use of granulocyte-colony stimulating factors (G-CSF) is permitted during investigational therapy at the discretion of the investigator. G-CSF or similar agents are strongly recommended following Grade 3 or 4 neutropenia of duration > 5 days or following any incidence of febrile neutropenia (ANC $< 1.0 \times 10^9$/L with temperature ≥ 38.5°C).

- Erythroid Growth Factors:

The use of erythroid-stimulating factors (eg, erythropoietin) is permitted at the discretion of the investigator based on American Society of Clinical Oncology and Food and Drug Administration (FDA) guidelines, or according to local guidelines [44].

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

5.7 Diet/Activity/Other Considerations

5.7.1 Diet

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

5.7.2 Contraception

Pembrolizumab and paclitaxel may have adverse effects on a fetus in utero. Furthermore, it is not known if pembrolizumab or paclitaxel has transient adverse effects on the composition of sperm. Therefore, non-pregnant, non-breast-feeding women may only be enrolled if they are willing to use 2 methods of birth control or are considered highly unlikely to conceive. Highly unlikely to conceive is defined as 1) surgically sterilized, or 2) postmenopausal (a woman who is $\geq$ 45 years of age and has not had menses for greater than 1 year will be considered postmenopausal), or 3) not heterosexually active for the duration of the study. The two birth control methods can either be two barrier methods or a barrier method plus a hormonal method to prevent pregnancy. Subjects within the pembrolizumab arm of the study should start using birth control from study Visit 1 throughout the study period up to 120 days after the last dose of study treatment. Subjects within the paclitaxel arm of the study should start using birth control from study Visit 1 throughout the study period up to 180 days after the last dose of study treatment.

The following are considered adequate barrier methods of contraception: diaphragm, condom (by the partner), copper intrauterine device, sponge, or spermicide as per local regulations or guidelines. Appropriate hormonal contraceptives will include any registered and marketed contraceptive agent that contains an estrogen and/or a progestational agent (including oral, subcutaneous, intrauterine, or intramuscular agents).

Abstinence is acceptable if this is the established and preferred contraception for the subject.

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study they must adhere to the contraception requirement (described above) for the duration of the study and during the follow-up period defined in Section 7.2.2, Reporting of Pregnancy and Lactation to the Sponsor. If there is any question that a subject will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

5.7.3 Use in Pregnancy

If a subject inadvertently becomes pregnant while on treatment with pembrolizumab or paclitaxel, the subject will immediately be removed from the study. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the Sponsor without delay and within 24 hours if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor. If a male subject impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to the Sponsor and followed as described above and in Section 7.2.2.

5.7.4 Use in Nursing Women

It is unknown whether pembrolizumab or paclitaxel are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, subjects who are breast-feeding are not eligible for enrollment. Specific additional information follows for individual agents used in this trial.

5.8 Subject Withdrawal/Discontinuation Criteria

5.8.1 Discontinuation of Treatment

Discontinuation of treatment does not represent withdrawal from the trial.

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

Section 6.0 - Trial Flow Chart and Section 7.1.5.3 – Discontinued Subjects Continuing to be Monitored in the Trial.

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 7.1.2.6.4 and Section 7.1.2.6.5 (exception if the Sponsor approves treatment continuation)
- Unacceptable adverse experiences as described in Section 5.2.1.2
- 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
- Investigator's decision to withdraw the subject
- Completion of 35 treatments (approximately 2 years) with pembrolizumab

  Note: The number of treatments is calculated starting with the first dose. Subjects who stop after receiving 35 doses may be eligible for retreatment if they progress after stopping trial treatment provided they meet the requirements detailed in Section 7.1.5.5. Subjects may be retreated in the Second Course Phase (Retreatment) for up to an additional 17 cycles (approximately 1 year).
- Discontinuation of treatment may be considered for subjects who have attained a confirmed CR and have been treated for at least 8 cycles (at least 24 weeks), receiving at least 2 doses of pembrolizumab beyond the date when the initial CR was declared.
- Subjects who stop pembrolizumab with stable disease (SD), PR, or CR, may be eligible for up to 1 year (17 cycles) of pembrolizumab if they experience disease progression after stopping pembrolizumab. This retreatment is termed the Second Course Phase (Retreatment) and is described in detail in Section 7.1.5.5.
- 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 adverse event monitoring (serious adverse events 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, as described in Section 7.2.3.1). Subjects who discontinue for reasons other than progressive disease 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 overall survival until death, withdrawal of consent, or the end of the study, whichever occurs first. 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.

Discontinuation of Study Therapy after CR

Discontinuation of treatment may be considered for subjects who have attained a confirmed CR that have been treated for at least 24 weeks with pembrolizumab and had at least two treatments with pembrolizumab beyond the date when the initial CR was declared. Subjects who then experience radiographic disease progression may be eligible for up to one year of additional treatment with pembrolizumab via the Second Course Phase at the discretion of the investigator if no cancer treatment was administered since the last dose of pembrolizumab, the subject meets the safety parameters listed in the Inclusion/Exclusion criteria, and the trial is open. Subjects will resume therapy at the same dose and schedule at the time of initial discontinuation. Additional details are provided in Section 7.1.5.5.

For subjects who are discontinued from treatment but continue to be monitored in the trial, see Section 6.0 – Trial Flow Chart, and Section 7.1.5.3 – Discontinued Subjects Continuing to be Monitored in the Trial for those procedures to be completed at each specified visit.

Subjects may be allowed to begin treatment again if deemed medically appropriate, unless the subject's treatment assignment has been unblinded by the investigator/delegate and/or non-study treating physician.

5.8.2 Withdrawal from the Trial

Subjects may withdraw from the trial at any time for any reason. If a subject withdraws from the trial, they will no longer receive treatment or be followed at scheduled protocol visits.

A subject must be withdrawn from the trial if:

- The subject or subject's legally acceptable representative withdraws consent from the trial.
- The subject is lost to follow-up.

Specific details regarding procedures to be performed at the time of withdrawal from the trial including 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. 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). Upon study completion, participants are discontinued and may be enrolled in a pembrolizumab extension study. Enrollment in the extension study is conditional on subject consent.

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, GCP and/or other applicable regulatory requirements, procedure-related problems or the number of discontinuations for administrative reasons is too high.

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

1. Quality or quantity of data recording is inaccurate or incomplete

2. Poor adherence to protocol and regulatory requirements

3. Incidence or severity of adverse drug reaction in this or other studies indicates a potential health hazard to subjects

4. Plans to modify or discontinue the development of the study drug

In the event of Sponsor decision to no longer supply study drug, ample notification will be provided so that appropriate adjustments to subject treatment can be made.

6.0 TRIAL FLOW CHART

6.1 Trial Flow Chart – Initial Treatment Phase for Pembrolizumab Arm

Trial Period:	Screening Phase	Treatment Cycles[a]						End of Treatment	Post-Treatment		
Treatment Cycle/Title:	Screening (Visit 1)	1	2	3	4	To be repeated beyond 6 cycles 5	6	Discon	Safety Follow-up	Follow Up Visits[b]	Survival Follow-up[c]
								At time of discon	30 days post discon	Every 6 weeks post discon	Every 12 weeks
Scheduling Window (Days)[d]:	-28 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	
PROs (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				
Height, Weight, and Vital Signs (T, P, RR, BP)[j]	X	X	X	X	X	X	X	X			
ECOG Performance Status	X[k]	X	X	X	X	X	X	X			
Post-study Anticancer Therapy Status									X	X	X
Survival Status[c]		←	-	-	-	-	-	-	-	→	X
Trial Treatment Administration											
Pembrolizumab[l]		X	X	X	X	X	X				
Laboratory Procedures/Assessments: Analysis performed by LOCAL laboratory											
Pregnancy Test – Urine or Serum β-HCG[m]	X										
PT/INR and aPTT[n]	X										
CBC with Differential[o]	X		X	X	X	X	X[o]	X	X[o]		
Chemistry Panel[o]	X		X	X	X	X	X[o]	X	X[o]		

Trial Period:	Screening Phase	Treatment Cycles[a]						End of Treatment	Post-Treatment		
Treatment Cycle/Title:	Screening (Visit 1)	1	2	3	4	To be repeated beyond 6 cycles 5	6	Discon	Safety Follow-up	Follow Up Visits[b]	Survival Follow-up[c]
								At time of discon	30 days post discon	Every 6 weeks post discon	Every 12 weeks
Urinalysis[o]	X										
T3, FT4 and TSH	X [o]		X		X		X		X		
Serum carcinoembryonic antigen (CEA)[p]	X			X		X					
Serum CA 19-9[p]	X			X		X					
HBsAg	X [q]										
Hep C Ab and HCV RNA	X [q]										
Laboratory Procedures/Assessments: Analysis performed by CENTRAL laboratory											
Pharmacokinetics[r]		X	X		X		X[r]				
Anti-Drug Antibodies (ADA)[r]		X	X		X		X[r]				
Blood for Genetic Analyses[s]		X									
Correlative Blood Samples (RNA)[t]		X	X			X		X			
Correlative Blood Samples (plasma)[t]		X	X					X			
Correlative Blood Samples (serum)[t]		X	X					X			
Efficacy Measurements											
Tumor Imaging[u]	X			X		X		X[v]		X	
Tumor Tissue Collection											
Archival and/or Newly-Obtained Tissue Collection	X[w]	----------X[w]----------						X[w]			

a. Unless otherwise specified, assessments/procedures are to be performed on Day 1 and prior to the first dose of treatment for each cycle.
b. In subjects who discontinued 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 blinded central radiologists' 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 blinded central radiologists' vendor, the subject should be contacted by telephone approximately every 12 weeks to assess for survival status. Updated survival status may be requested by the Sponsor at any time during the course of the study. Upon Sponsor notification, all participants who do not/will not have a scheduled study visit or study contact during the Sponsor-defined time period will be contacted for their survival status (excluding participants that have a death event previously recorded).
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 (e.g., within 28 days prior to the first dose of trial treatment). Pre-screening informed consent may be signed prior to the Screening Period specified above in the Trial Flow Chart (-28 to -1 days) to allow the submission of archive tumor tissue sample for determination of PD-L1 status and is expected to comply with all IRB/EC requirements.

Trial Period:	Screening Phase	Treatment Cycles[a]						End of Treatment	Post-Treatment		
						To be repeated beyond 6 cycles					
Treatment Cycle/Title:	Screening (Visit 1)	1	2	3	4	5	6	Discon	Safety Follow-up	Follow Up Visits[b]	Survival Follow-up[c]
								At time of discon	30 days post discon	Every 6 weeks post discon	Every 12 weeks

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.
g. Prior medications – Record all medications taken within 30 days of screening visit. 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 and ECIs occurring within 30 days after the last dose of trial treatment. Report all SAEs (related and unrelated to trial treatment) occurring up until 90 days after the last dose of trial treatment or 30 days following last dose of trial treatment if the subject initiates new anticancer therapy, whichever comes first. Afterwards, report only SAEs and ECIs that are related to trial treatment.
i. It is most relevant and strongly recommended that Patient Reported Outcomes (PROs) are administered prior to drug administration, adverse event evaluation and disease status notification starting with the EQ-5D, followed by EORTC QLQ-C30 and EORTC QLQ-ST022; an exception to this recommendation may occur at the treatment discontinuation visit where patients may have already been notified of their disease status or an AE evaluation is known prior to them arriving to the clinic. All PROs are to be performed at Cycle 1, Cycle 2, Cycle 3, Cycle 4, Cycle 5, Cycle 7, and Cycle 9. After Week 24, PROs are to be performed every 6 weeks (conducted at corresponding study visit) 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 PROs, the MISS_MODE form must be completed to capture the reason the assessment was not performed.
j. Height will be measured at Visit 1 only. Vitals Signs include temperature, pulse, respiratory rate, and blood pressure.
k. ECOG PS should be assessed within 3 days prior to the first dose of trial treatment.
l. Pembrolizumab should be administered on Day 1 of each 3-week cycle after all procedures/assessments have been completed.
m. Female subjects of childbearing potential should have a negative urine or serum pregnancy test within 72 hours prior to receiving the first dose of study therapy. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
n. Coagulation factors (PT/INR and aPTT) should be tested as part of the screening procedures for all subjects.
o. 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 and Chemistry panel are to be repeated every 2 cycles after Cycle 6 (e.g., Cycle 8-Day 1, Cycle 10-Day 1). 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.
p. Serum CEA and CA 19-9 should be collected at screening (baseline) and every 6 weeks (conducted at corresponding study visits) until study treatment discontinuation.
q. Tests will be performed by a central laboratory only if the local laboratory is unable to perform this service. The need for additional testing due to positive test results will be at the discretion of the investigator.
r. PK and anti-pembrolizumab antibody will be collected for all subjects who receive pembrolizumab monotherapy. Pre-dose trough PK and anti-pembrolizumab antibody samples will be collected at Cycles 1, 2, 4, 6, and 8 and every 4 cycles thereafter. All pre-dose trough samples should be drawn within 24 hours before infusion of pembrolizumab.
s. 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. If the planned genetic analysis is not approved, but FBR is approved and consent is given, this sample will be collected for the purpose of FBR. Detailed instructions for the collection and management of specimens are provided in the Procedures Manual and Section 12.2.
t. Whole blood sample for correlative studies should be collected pre-dose on Day 1 of Cycle 1, 2, and 5, or at time of discontinuation. Blood for serum and blood for plasma to

Trial Period:	Screening Phase	Treatment Cycles[a]						End of Treatment	Post-Treatment		
Treatment Cycle/Title:	Screening (Visit 1)	1	2	3	4	To be repeated beyond 6 cycles 5	6	Discon	Safety Follow-up	Follow Up Visits[b]	Survival Follow-up[c]
								At time of discon	30 days post discon	Every 6 weeks post discon	Every 12 weeks

be collected pre-dose on Day 1 of Cycle 1, 2, or at time of discontinuation. Leftover RNA, plasma and serum will be stored at the end of the study for future biomedical research if the subject consents to future biomedical research. See Procedures Manual.

u. Baseline tumor imaging will be performed within 14 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) or earlier if clinically indicated and will continue to be performed every 6 weeks (± 7 days) regardless of any treatment delays. Imaging timing should follow calendar days. On-study scans should be submitted immediately to the blinded central radiologists' vendor.

v. In subjects who discontinue study therapy without centrally verified disease progression, a radiologic evaluation should be performed at the time of treatment discontinuation (i.e., 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.

w. Baseline tumor 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. An optional newly obtained core or excisional biopsy (FNA not adequate) is requested at any post-treatment time point during the study (preference would be as close to dosing at Week 12 as possible). A biopsy is also requested at the time of discontinuation for PD, but will not be required. Endoscopic biopsies are permitted. Any leftover tumor will be stored for future biomedical research if the subject signs the FBR consent.

6.2 Trial Flow Chart – Initial Treatment Phase for Paclitaxel Arm

Trial Period:	Screening Phase	Treatment Cycles[a] Continue to Repeat Cycles 1 and 2 until Discon						End of Treatment	Post-Treatment		
Treatment Cycle/Title:	Screening (Visit 1)	Cycle 1 Day 1	Cycle 1 Day 8	Cycle 1 Day 15	Cycle 2 Day 1	Cycle 2 Day 8	Cycle 2 Day 15	Discon	Safety Follow-up	Follow Up Visits [b]	Survival Follow-up [c]
								At time of discon	30 days post discon	Every 6 weeks post discon	Every 12 weeks
Scheduling Window (Days) [d]:	-28 to -1							± 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	
PROs (HRQoL Measures) [i]		X			X		X	X	X		
12-Lead ECG (Local)	X										
Full Physical Examination	X							X			
Directed Physical Examination		X	X	X	X	X	X				
Height, Weight, and Vital Signs (T, P, RR, BP)[j]	X	X	X	X	X	X	X	X			
ECOG Performance Status	X[k]	X	X	X	X	X	X	X			
Post-study Anticancer Therapy Status									X	X	X
Survival Status[c]		←								→	X
Trial Treatment Administration											
Paclitaxel[l]		X	X	X	X	X	X				
Laboratory Procedures/Assessments: Analysis performed by LOCAL laboratory											
Pregnancy Test – Urine or Serum β-HCG[m]	X										
PT/INR and aPTT [n]	X										
CBC with Differential[o]	X		X	X	X	X	X	X	X		
Chemistry Panel[o]	X		X	X	X	X	X	X	X		
Urinalysis [o]	X										
T3, FT4 and TSH	X[o]		X				X		X		

Trial Period:	Screening Phase	Treatment Cycles[a] Continue to Repeat Cycles 1 and 2 until Discon						End of Treatment	Post-Treatment		
Treatment Cycle/Title:	Screening (Visit 1)	Cycle 1 Day 1	Cycle 1 Day 8	Cycle 1 Day 15	Cycle 2 Day 1	Cycle 2 Day 8	Cycle 2 Day 15	Discon	Safety Follow-up	Follow Up Visits [b]	Survival Follow-up [c]
								At time of discon	30 days post discon	Every 6 weeks post discon	Every 12 weeks
Serum carcinoembryonic antigen[p]	X						X				
Serum CA19-9[p]	X						X				
HBsAg	X [q]										
Hep C Ab and HCV RNA	X [q]										
Laboratory Procedures/Assessments: Analysis performed by CENTRAL laboratory											
Blood for Genetic Analyses[r]		X									
Correlative Blood Samples (RNA)[s]		X			X			X			
Correlative Blood Samples (plasma)[s]		X			X			X			
Correlative Blood Samples (serum)[s]		X			X			X			
Efficacy Measurements											
Tumor Imaging[t]	X						X[t]	X[u]		X	
Tumor Tissue Collection											
Archival and/or Newly-Obtained Tissue Collection	X[v]	----------X[v]----------						X[v]			

a. Unless otherwise specified, assessments/procedures are to be performed on Day 1 and prior to the first dose of treatment for each cycle.
b. In subjects who discontinued 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 blinded central radiologists' 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 blinded central radiologists' vendor, the subject should be contacted by telephone approximately every 12 weeks to assess for survival status. Updated survival status may be requested by the Sponsor at any time during the course of the study. Upon Sponsor notification, all participants who do not/will not have a scheduled study visit or study contact during the Sponsor-defined time period will be contacted for their survival status (excluding participants that have a death event previously recorded).
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 from (e.g., within 28 days prior to the first dose of trial treatment). Pre-screening informed consent may be signed prior to the Screening Period specified above in the Trial Flow Chart (-28 to -1 days) to allow the submission of archive tumor tissue sample for determination of PD-L1 status and is expected to comply with all IRB/EC requirements.
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 provide the Procedures Manual.
g. Prior medications – Record all medications taken within 30 days of screening visit. 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.

Trial Period:	Screening Phase	Treatment Cycles[a] Continue to Repeat Cycles 1 and 2 until Discon						End of Treatment	Post-Treatment		
Treatment Cycle/Title:	Screening (Visit 1)	Cycle 1 Day 1	Cycle 1 Day 8	Cycle 1 Day 15	Cycle 2 Day 1	Cycle 2 Day 8	Cycle 2 Day 15	Discon	Safety Follow-up	Follow Up Visits [b]	Survival Follow-up [c]
								At time of discon	30 days post discon	Every 6 weeks post discon	Every 12 weeks

h. Record all AEs and ECIs occurring within 30 days after the last dose of trial treatment. Report all SAEs (related and unrelated to trial treatment) occurring up until 90 days after the last dose of trial treatment or 30 days following last dose of trial treatment if the subject initiates new anticancer therapy, whichever comes first. Afterwards, report only SAEs and ECIs that are related to trial treatment.

i. It is most relevant and strongly recommended that Patient Reported Outcomes (PROs) are administered prior to drug administration, adverse event evaluation and disease status notification starting with the EQ-5D, followed by EORTC QLQ-C30, EORTC QLQ-ST022 an exception to this recommendation may occur at the treatment discontinuation visit where patients may have already been notified of their disease status or an AE evaluation is known prior to them arriving to the clinic. All PROs are to be performed prior to Cycle 1-Day 1, Cycle 2-Day 1, Cycle 2-Day 15, Cycle 3-Day 8, Cycle 4-Day 1 and every 6 weeks thereafter (conducted at corresponding study visit) 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 PROs, the MISS_MODE form must be completed to capture the reason the assessment was not performed.

j. Height will be measured at Visit 1 only. Vitals Signs include temperature, pulse, respiratory rate, and blood pressure.

k. ECOG PS should be assessed within 3 days prior to the first dose of trial treatment.

l. Paclitaxel should be administered on Day 1, 8, and 15 of each 28-day (4-week) cycle after all procedures/assessments have been completed.

m. Female subjects of childbearing potential should have a negative urine or serum pregnancy test within 72 hours prior to receiving the first dose of study therapy. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

n. Coagulation factors (PT/INR and aPTT) should be tested as part of the screening procedures for all subjects.

o. 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 must be collected within 48 hours prior to the scheduled dose administration of paclitaxel. CBC with differential and chemistry panel should be completed at every study visit, except for unscheduled visits (unless clinically indicated). 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.

p. Serum CEA and CA19-9 should be collected at screening (baseline) and every 6 weeks (conducted at corresponding study visits) until study treatment discontinuation.

q. Tests will be performed by a central laboratory only if the local laboratory is unable to perform this service. The need for additional testing due to positive test results will be at the discretion of the investigator.

r. This sample should be drawn for planned analysis of the association between genetic variants in DNA and drug response. If there is either a documented law or regulation prohibiting collection, or if the IRB/IEC does not approve the collection of the sample for these purposes, then this sample will not be collected at that site. If the sample is collected, leftover extracted DNA will be stored for future biomedical research if the subject signs the FBR consent. If the planned genetic analysis is not approved, but FBR is approved and consent is given, this sample will be collected for the purpose of FBR. 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 pre-dose on Day 1 of Cycle 1, 2, and 5, or at time of discontinuation. Blood for serum and blood for plasma to be collected pre-dose on Day 1 of Cycle 1, 2, or at time of discontinuation. Leftover RNA, plasma and serum will be stored at the end of the study for future biomedical research if the subject consents to future biomedical research. See Procedures Manual.

t. Baseline tumor imaging will be performed within 14 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) or earlier if clinically indicated and will continue to be performed every 6 weeks (± 7 days) regardless of any treatment delays. Imaging timing should follow calendar days. On-study scans should be submitted immediately

Trial Period:	Screening Phase	Treatment Cycles[a]						End of Treatment	Post-Treatment		
		Continue to Repeat Cycles 1 and 2 until Discon									
Treatment Cycle/Title:	Screening (Visit 1)	Cycle 1 Day 1	Cycle 1 Day 8	Cycle 1 Day 15	Cycle 2 Day 1	Cycle 2 Day 8	Cycle 2 Day 15	Discon	Safety Follow-up	Follow Up Visits [b]	Survival Follow-up [c]
								At time of discon	30 days post discon	Every 6 weeks post discon	Every 12 weeks

to the blinded central radiologists' vendor.

u. In subjects who discontinue study therapy without centrally verified disease progression, a radiologic evaluation should be performed at the time of treatment discontinuation (i.e., 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.

v. Baseline tumor 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. An optional newly obtained core or excisional biopsy (FNA not adequate) is requested at any post-treatment time point during the study (preference would be as close to dosing at Week 12 as possible). A biopsy is also requested at the time of discontinuation for PD, but will not be required. Endoscopic biopsies are permitted. Any leftover tumor will be stored for future biomedical research if the subject signs the FBR consent.

6.3 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	Discon At time of discon	Safety Follow-up 30 days post discon	Follow Up Visits[b] Every 6 weeks post discon	Survival Follow-up[c] Every 12 weeks
Scheduling Window (Days)[d]:		± 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			
ECOG Performance Status	X[i]	X	X	X	X	X	X			
Pembrolizumab Administration[j]	X	X	X	X	X	X				
Post-study Anticancer Therapy Status								X	X	X
Survival Status[c]	<----------								---------->	X
Laboratory Procedures/Assessments: Analysis performed by LOCAL laboratory										
Pregnancy Test – Urine or Serum β-HCG[k]	X									
PT/INR and aPTT[l]	X									
CBC with Differential[m]	X	X	X	X	X	X[m]	X	X		
Chemistry Panel[m]	X	X	X	X	X	X[m]	X	X		
Urinalysis[m]	X									
T3, FT4 and TSH[m]	X		X		X			X		
Efficacy Measurements										
Tumor Imaging[n]	X		X			X	X[o]		X	

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 ± 3 days) until (1) the start of new anti-cancer treatment, (2) disease progression as assessed by the blinded central radiologists' 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 blinded central radiologists' vendor, the subject should be contacted by telephone approximately every 12 weeks to assess for survival status. Updated survival status may be requested by the Sponsor at any time during the course of the study. Upon Sponsor notification, all participants who do not/will not have a scheduled study visit or study contact during the Sponsor-defined time period will be contacted for their

Trial Period:	Treatment Cycles[a]						End of Treatment	Post-Treatment		
							Discon	Safety Follow-up	Follow Up Visits[b]	Survival Follow-up[c]
Treatment Cycle:	1	2	3	4	5	Cycle 6 and beyond	At time of discon	30 days post discon	Every 6 weeks post discon	Every 12 weeks
Scheduling Window (Days)[d]:		± 3	± 3	± 3	± 3	± 3	± 3	± 7	± 7	± 7

survival status (excluding participants that have a death event previously recorded).

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 (~ 2 years) on pembrolizumab for reasons other than disease progression or intolerability may restart trial treatment if they meet the criteria specified in Section 7.1.5.5.

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 and ECIs occurring within 30 days after the last dose of trial treatment. Report all SAEs (related and unrelated to trial treatment) occurring up until 90 days after the last dose of trial treatment or 30 days following last dose of trial treatment if the subject initiates new anti-cancer therapy, whichever comes 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. ECOG PS should be assessed within 3 days prior to the first dose of trial treatment in Second Course Phase.

j. Subjects who restart treatment should resume at the same dose and schedule which they were receiving prior to discontinuation.

k. Female subjects of childbearing potential should have a negative urine or serum pregnancy test within 72 hours prior to receiving the first dose of study therapy. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

l. Coagulation factors (PT/INR and aPTT) should be tested as part of the screening procedures for all subjects.

m. Laboratory tests for determining eligibility for retreatment are to be performed within 10 days prior to the first retreatment dose of pembrolizumab. 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 6. 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.

n. 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 treatment 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. See Section 7.1.2.6.3

o. In subjects who discontinue study therapy without confirmed disease progression, a radiologic evaluation should be performed at the time of treatment discontinuation (i.e., 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.

7.0 TRIAL PROCEDURES

7.1 Trial Procedures

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

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

7.1.1 Administrative Procedures

7.1.1.1 Informed Consent

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

7.1.1.1.1 General Informed Consent

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

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

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

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

The informed consent will adhere to IRB/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 Future Biomedical Research. A copy of the informed consent will be given to the subject.

7.1.1.2 Inclusion/Exclusion Criteria

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

7.1.1.3 Subject Identification Card

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

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

7.1.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee. Medical history will include all active conditions, and any condition diagnosed within the prior 10 years that are considered to be clinical significant by the investigator. Details regarding the subject's gastric or GEJ adenocarcinoma will be recorded separately and not listed as medical history.

Please note that if the patient has lost at least 6.8 kg (15 lbs.) over the three months prior to screening, "weight loss" should be entered as an active condition on the Medical History. As well, any autoimmune disorders, regardless of onset date, should be recorded.

7.1.1.4.1 Disease Details

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

7.1.1.5 Prior and Concomitant Medications Review

7.1.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the subject within 30 days before starting the trial. Details regarding the subject's gastric or GEJ adenocarcinoma medications will be recorded separately and not listed as prior medications.

7.1.1.5.2 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 form until the Safety Follow-up Visit. All medications related to reportable SAEs and ECIs should be recorded as defined in Section 7.2.

7.1.1.6 Assignment of Screening Number

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

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

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

7.1.1.7 Assignment of Treatment/Randomization Number

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

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

Drug administration should occur within 3 days from assignment of a randomization number.

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

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

Administration of trial medication will be monitored by the investigator and/or trial staff.

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 study and during the follow-up period according to NCI CTCAE Version 4.0 (see Section 12.5). Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

All AEs of unknown etiology associated with study treatment exposure should be evaluated to determine if it is possibly an event of a potentially immunologic etiology; see Section 5.6.1.

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 clinical designee will perform a complete physical exam during the screening period. Clinically significant abnormal findings should be recorded as medical history. A full physical exam should be performed as specified in the Trial Flow Chart. 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/visits that do not require a full physical exam per the Trial Flow Chart, the investigator or qualified designee will perform a directed physical exam as clinically indicated prior to dosing on Day 1 of each treatment cycle for the pembrolizumab arm and on Days 1, 8, and 15 of each treatment cycle for the paclitaxel arm. New clinically significant abnormal findings should be recorded as AEs.

7.1.2.3 Vital Signs

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

7.1.2.4 12-Lead Electrocardiogram

A standard 12-lead ECG will be performed using local standard procedures once at screening. Clinically significant abnormal findings should be recorded as medical history. Additional time points may be performed as clinically necessary.

7.1.2.5 Eastern Cooperative Oncology Group (ECOG) Performance Status

The investigator or qualified designee will assess ECOG performance status (see Section 12.4) at screening, prior to dosing of trial treatment, and at discontinuation of trial treatment for both treatment arms, as specified in the Trial Flow Chart.

7.1.2.6 Tumor Imaging and Assessment of Disease

Processes for image collection and transmission to the central vendor can be found in the Procedure Manual. The Site Imaging Manual will provide details on acquisition parameters and image transmission practices required for this trial.

7.1.2.6.1 Initial Tumor Imaging

To meet screening criteria, initial tumor imaging must be performed within 14 days prior to randomization. This scan will be considered the baseline assessment for the study. The site study team must review pre-trial images to confirm the subject has at least one target lesion per standard RECIST 1.1.

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 14 days prior to randomization.

7.1.2.6.2 Tumor Imaging During Trial

The first on-study imaging assessment should be performed at 6 weeks (42 days ± 7 days) from the date of randomization. Subsequent imaging should be performed every 6 weeks (42 days ± 7 days) or more frequently if clinically indicated. Imaging timing should follow calendar days and should not be adjusted for delays in cycle starts. Imaging should continue to be performed until disease progression verified by the central imaging vendor (unless the site principal investigator elects to continue treatment and follow irRECIST), the start of new anticancer treatment, withdrawal of consent, or death, whichever occurs first. All supplemental imaging must be submitted to the central imaging vendor.

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

Per RECIST 1.1, PR and CR should be confirmed by a repeat tumor imaging assessment obtained 4 weeks or longer from the date the response was first documented. The tumor imaging performed to confirm a response may be performed, at the earliest, 4 weeks after the first indication of a response, or at the next scheduled scan (i.e., 6 weeks later), whichever is clinically indicated. Subjects will then return to regular scheduled imaging every 6 weeks, starting with the next scheduled imaging time point. Subjects who obtain a confirmation scan do not need to undergo the next scheduled tumor imaging if it is <4 weeks later; tumor imaging may resume at the subsequent scheduled imaging time point.

At the time of the initial PD by RECIST 1.1 imaging scans should be sent to the central vendor to verify PD. If PD is verified, the investigator may choose to continue treatment if

the patient is clinically stable and repeat imaging at least 4 weeks after the first tumor imaging indicating PD to confirm PD (by the site) and then follow irRECIST.

Per irRECIST (Section 7.1.2.6.5), 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 7.1.2.6.5. Subjects who obtain a confirmation scan do not need to undergo the next scheduled tumor imaging if it is <4 weeks later; tumor imaging may resume at the subsequent scheduled imaging time point if clinically stable. Subjects who have confirmed disease progression, as assessed by the site, will discontinue trial treatment. Exceptions are detailed in Section 7.1.2.6.5.

7.1.2.6.3 Second Course (Retreatment Tumor Imaging)

Tumor imaging must be performed within 21 days prior to restarting treatment with pembrolizumab. Imaging should continue to be performed every 6 weeks (42 days ± 7 days) after the restart of treatment 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. Local reading (investigator assessment with site radiology reading) will be used to determine eligibility. All Second Course imaging should be submitted to the imaging Contract Research Organization (iCRO) for quality control, storage, and possible retrospective review.

For participants who discontinue Second Course study intervention, tumor imaging should be performed at the time of intervention discontinuation (±4-week window). If previous imaging was obtained within 4 weeks prior to the date of discontinuation, then imaging at intervention discontinuation is not mandatory. For participants who discontinue study intervention due to documented disease progression, this is the final required tumor imaging.

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

7.1.2.6.4 RECIST 1.1 Assessment of Disease

RECIST 1.1 will be used by blinded independent central review (BICR) as the primary measure for assessment of tumor response, date of disease progression, and as a basis for all protocol guidelines related to disease status (e.g., 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 target lesions in total and 5 per organ, if clinically relevant, to enable a broader sampling of tumor burden. Initial tumor imaging showing site-assessed PD should be submitted to the 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 2 illustrates the imaging flow involving verification of PD for clinically stable subjects.

7.1.2.6.5 irRECIST Assessment of Disease

irRECIST is RECIST 1.1 adapted as described below to account for the unique tumor response seen with immunotherapeutic drugs. irRECIST will be used by the site investigator/local radiology reviewers to assess tumor response and progression, and to make treatment decisions. These 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 tumor flare in the first few months after the start of immunotherapy, and then experience subsequent disease response. Subjects that are deemed clinically unstable are not required to have repeat tumor imaging for confirmation of PD. Tumor flare includes any of the following scenarios:

- Worsening of existing target lesion(s)
- Worsening of existing nontarget 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 principal investigator whether to continue a subject on trial medication until repeat imaging is obtained (using irRECIST for subject management (see Table 7 and Figure 2). This clinical judgment decision by the site investigator should be based on the subject's overall clinical condition, including performance status, clinical symptoms, and laboratory data. Subjects may receive trial medication and the tumor assessment should be repeated ≥4 weeks later in order to confirm PD by irRECIST per site assessment. Clinical stability is defined as the following:

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

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

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

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

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

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

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

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

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

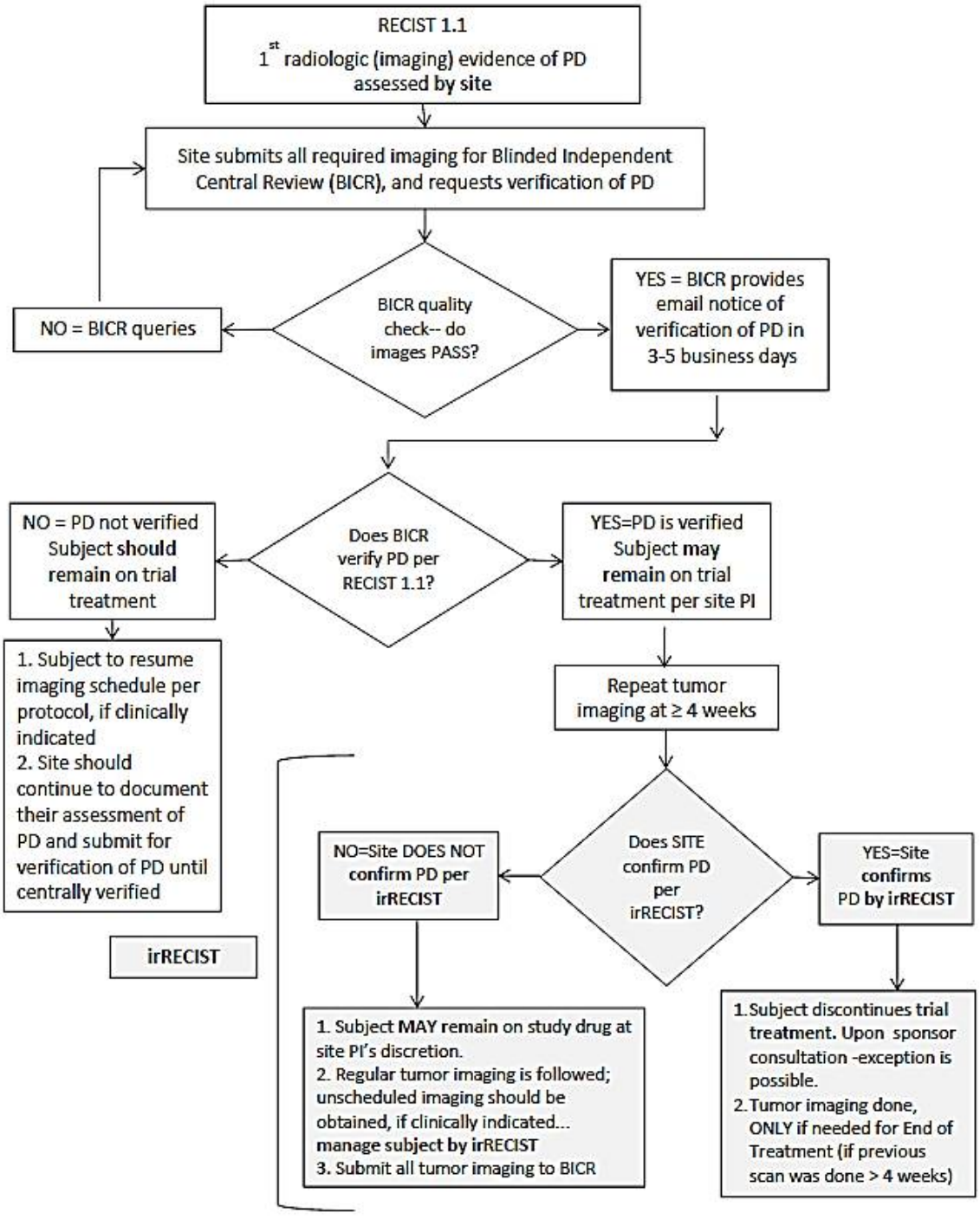
NOTE: If a subject has confirmed radiographic progression (i.e., 2 scans at least 4 weeks apart demonstrating PD) per irRECIST, but the subject is achieving a clinically meaningful benefit, and there is no further increase in the tumor burden at the confirmatory tumor imaging, an exception to continue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

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

Table 7 Imaging and Treatment after First Radiologic Evidence of Progressive Disease (PD)

	Clinically Stable		**Clinically Unstable**	
	Imaging	**Treatment**	**Imaging**	**Treatment**
First radiologic evidence of PD, which has been verified by the central imaging vendor	Repeat imaging at site at ≥ 4 weeks to confirm PD	May continue trial treatment at the local site investigator's discretion while awaiting confirmatory tumor imaging by site by irRECIST	Repeat imaging at ≥ 4 weeks to confirm PD per physician discretion only	Discontinue treatment
Repeat tumor imaging confirms PD by irRECIST at the local site	No additional imaging required	Discontinue treatment (exception is possible upon consultation with Sponsor).	No additional imaging required	Not applicable
Repeat tumor imaging shows SD, PR, or CR by irRECIST at the local site	Continue regularly scheduled imaging assessments every 6 weeks	Continue trial treatment at the local site investigator's discretion	Continue regularly scheduled imaging assessments every 6 weeks	May restart trial treatment if condition has improved and/or clinically stable per investigator's discretion. Next tumor image should occur according to the regular imaging schedule.

Figure 2 Imaging and Treatment for Clinically Stable Subjects Treated with Pembrolizumab after First Radiologic Evidence of PD Assessed by the Site



7.1.2.7 Tumor Tissue Collection and Correlative Blood Sampling

Participation in this trial will be dependent upon supplying a tumor tissue specimen. Newly obtained endoscopic biopsy specimens are preferred to archived samples and formalin-fixed, paraffin-embedded (FFPE) block specimens are preferred to slides. The specimen will be evaluated at a central laboratory facility for expression status of PD-L1, and only PD-L1 positive subjects will be eligible for this trial.

Note: A fine needle aspirate (FNA) or cytologic specimen will not be acceptable. Newly obtained endoscopic biopsy specimen or archived tissue should be submitted in the condition described in the Procedure Manual. If there is an existing specimen obtained with surgical resection or core needle biopsy, these can be submitted. Newly-obtained specimens are defined as FFPE-preserved blocks of tissue collected up to 6 weeks (42 days) prior to Day 1.

Collection of an archived tissue sample will also be requested (where available) to support evaluation of the clinical utility of PD-L1 assessment in newly obtained vs. archived tissue samples; however, a subject will not be precluded from participating in the study if an archived tissue sample is not available for collection or is otherwise insufficient for analysis.

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

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

7.1.2.8 Blood Collections – Samples for Correlative and Genetic Analyses

Additional biomarker research to identify factors important for pembrolizumab therapy may also be pursued. For example, tumor and blood samples (including serum and plasma) from this study may undergo proteomic, genomic, metabolomics, and transcriptional analyses. Additional research may evaluate factors important for predicting responsiveness or resistance to pembrolizumab therapy and other immunologic targets.

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.

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

Details regarding time points for blood collection are outlined in the Trial Flow Chart – Section 6.1. Further details can also be found in Section 4.2.3.4.3 and further detailed instructions for tissue collection, processing and shipment are provided in the Procedures Manual.

7.1.2.9 Patient Reported Outcomes (PRO)

The EuroQol EQ-5D, EORTC QLQ-C30, and EORTC QLQ-STO22 questionnaires will be administered by trained study site personnel and completed by subjects. It is strongly recommended that the EORTC QLQ-C30, EORTC QLQ-STO22 and EuroQol EQ-5D is completed by the patient prior to drug administration, adverse event evaluation and disease status notification; an exception to this recommendation may occur at the treatment discontinuation visit. PROs will be administrated in the following order: EuroQol EQ-5D 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 Procedure Manual.

7.1.3.1 Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

Laboratory tests for hematology, chemistry, and urinalysis are specified in Table 8.

Table 8 Laboratory Tests

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

Hematology	Chemistry	Urinalysis	Other
a. Perform on women of childbearing potential only. Serum pregnancy test is preferred but urine test can be considered if serum not appropriate. 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. 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 for both arms of the study. After Cycle 1, pre-dose laboratory procedures can be conducted up to 72 hours prior to dosing for the pembrolizumab arm. For subjects within the paclitaxel arm, after Cycle 1 Day 1, the pre-infusion data may not be older than 48 hours. Results must be reviewed by the investigator or qualified designee and found to demonstrate adequate organ functions prior to each dose of trial treatment.

There may be instances when sites are unable to obtain the thyroid function testing results prior to scheduled dosing. After Cycle 1, review of thyroid function tests (FT3, FT4 and TSH) results after dosing is acceptable.

7.1.3.2 Serum/Urine β-hCG

All women who are being considered for participation in the trial, and who are not surgically sterilized or postmenopausal, will be tested for pregnancy within 72 hours of receiving the first dose of study therapy, and must be excluded in the event of a positive or borderline-positive test result. If a urine test is positive or borderline a serum β-HCG test will be required.

7.1.3.3 Pharmacokinetic/Pharmacodynamic Evaluations

To evaluate the immunogenicity and exposure of pembrolizumab in this indication, sample collections for analysis of anti-pembrolizumab antibodies (ADA) and PK are currently planned as shown in the Trial Flow Chart (Section 6.1). Further analysis may be performed, if required. If ongoing PK and/or ADA sampling is deemed to be unnecessary by the Sponsor, it may be reduced or discontinued.

7.1.3.3.1 Blood Collection for Serum MK-3475

Sample collection, storage and shipment instructions for serum PK samples will be provided in the Procedures Manual. PK samples should be drawn according to the PK collection schedule for subjects who receive pembrolizumab.

7.1.3.3.2 Blood Collection for Anti-pembrolizumab Antibodies

Sample collection, storage and shipment instructions for anti- pembrolizumab antibody samples will be provided in the Procedures Manual. Anti- pembrolizumab antibody samples should be drawn according to the ADA collection schedule for subjects who receive pembrolizumab. Simultaneous PK sampling is required for interpretation of ADA analysis.

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 Procedure Manual.

7.1.3.5 Future Biomedical Research Samples

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

- Leftover DNA
- Leftover RNA
- Leftover plasma and serum from biomarker studies
- Leftover tumor tissue

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 arm who a) attain a CR or b) complete 35 administrations (approximately 2 years) of treatment with pembrolizumab may discontinue treatment with the option of restarting treatment if they meet the criteria specified in Section 7.1.5.5. After discontinuing treatment following assessment of CR or 35 administrations (~ 2 years) of treatment, these subjects should return to the site for a Safety Follow-up Visit (described in Section 7.1.5.4.1) and then proceed to the Follow-up Period of the study (described in Section 7.1.5.4.2).

7.1.4.1.1 Withdrawal From Future Biomedical Research

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

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

7.1.4.2 Subject Blinding/Unblinding

This is an open label trial; there is no blinding for this trial.

7.1.4.3 Calibration of Critical Equipment

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

Critical Equipment for this trial includes:

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

See protocol-specified guidance in the Administrative Binder, Procedures Manual, Site Imaging Manual (SIM) and irRECIST Tip Sheet.

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

7.1.5.1.1 Pre-screening Period

The Pre-screening period may be utilized by subjects to determine biomarker eligibility based on PD-L1 status using an archival tumor biopsy sample. After providing a pre-screening consent, subjects will be assigned a screening number. Characterization of PD-L1 status will be performed at a pre-screening visit for subjects with an available archival tumor biopsy sample.

Subjects that do not have an archival tumor biopsy sample available must provide written consent for the main study before the tumor biopsy or any other protocol-specified procedures can occur. These subjects will not enter the pre-screening period as eligibility based on PD-L1 expression will be determined in the main study screening period.

7.1.5.1.2 Screening Period

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

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

- Laboratory tests are to be performed within 10 days prior to the first dose of trial treatment; ECOG PS should be assessed within 3 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 serum test is not appropriate.
- Baseline tumor imaging will be performed within 14 days prior to randomization for all subjects. 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.

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 – Trial Flow Chart. Specific procedure-related details are provided above in Section 7.1 – Trial Procedures.

7.1.5.3 Discontinued Subjects Continuing to be Monitored in the Trial

The Discontinuation Visit should occur at the time study treatment is discontinued for any reason. If the Discontinuation Visit occurs 30 days from the last dose of study treatment, at the time of the mandatory Safety Follow up Visit, procedures do not need to be repeated. Visit requirements are outlined in Section 6.0 – Trial Flow Chart. Specific procedure-related details are provided above in Section 7.1 – Trial Procedures. Additional details regarding subject withdrawal and discontinuation are presented in Section 5.8.

7.1.5.4 Post-Treatment

7.1.5.4.1 Safety Follow-up

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 anti-cancer treatment, whichever comes first.

Participants who are eligible for retreatment with pembrolizumab (as described in Section 7.1.5.5) may have up to 2 safety follow-up visits, 1 after the Treatment Period and 1 after the Second Course Phase.

7.1.5.4.2 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 every 6 weeks (42 ± 7 days) by radiologic imaging 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 anti-cancer therapy, disease progression determined by the blinded central radiologists' vendor, death, or at end of study. Information regarding post-study anti-cancer treatment will be collected if new treatment is initiated.

Subjects who are eligible to receive retreatment with pembrolizumab according to the criteria in Section 7.1.5.5 will move from the Follow-up Phase to the Second Course Phase when they experience disease progression. Details are provided in Section 6.2 – Trial Flow Chart for retreatment with pembrolizumab.

7.1.5.4.3 Survival Follow-up

Once a subject experiences confirmed disease progression confirmed by central review or starts a new anti-cancer therapy, the subject moves 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 study, whichever occurs first.

7.1.5.4.4 Survival Status

To ensure current and complete survival data are 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 eDMC safety review, efficacy interim analysis, 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 previously recorded a death he collection tool).

7.1.5.5 Second Course Phase (Retreatment Period)

Subjects on the pembrolizumab arm who stop treatment with SD or better may be eligible for up to one year of additional pembrolizumab therapy if they progress after stopping study treatment. This retreatment is termed the Second Course Phase of this study and is only available if the trial remains open and the subject meets the following conditions:

- **Either**
    - Stopped initial treatment with pembrolizumab after attaining an investigator-determined confirmed CR according to RECIST 1.1
        - Was treated for at least 24 weeks with pembrolizumab before discontinuing therapy
        - Received at least two treatments with pembrolizumab beyond the date when the initial CR was declared

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

- **AND**
    - Experienced an investigator-determined radiographic disease progression after stopping their initial treatment with pembrolizumab
    - Did not receive any anti-cancer treatment since the last dose of pembrolizumab
    - Has a performance status of 0 or 1 on the ECOG Performance Scale
    - Demonstrates adequate organ function as detailed in Section 5.1.2
    - Female subject of childbearing potential should have a negative serum or urine pregnancy test within 72 hours prior to receiving retreatment with study medication.
    - Female subject of childbearing potential should be willing to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days (Section 5.7.2). Subjects of child bearing potential are those who have not been surgically sterilized or have been free from menses for > 1 year.
    - Male subject should agree to use an adequate method of contraception starting with the first dose of study therapy through 120 days.

- Does not have a history or current evidence of any condition, therapy, or laboratory abnormality that might 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.

Subjects who restart treatment will be retreated at the same dose frequency as when they last received pembrolizumab. Treatment will be administered for up to one additional year.

Visit requirements for the second course phase are outlined in Section 6.3 – Trial Flow Chart – Second Course Phase – Retreatment with pembrolizumab.

Subjects on the paclitaxel arm are not eligible for this course of therapy.

7.2 Assessing and Recording Adverse Events

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

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

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

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

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

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

section 7.2.3.1. The investigator will make every attempt to follow all subjects with non-serious adverse events for outcome.

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

Adverse events will not be collected for subjects during the pre-screening period (for determination of archival tissue status) as long as that subject has not undergone any protocol-specified procedure or intervention. If the subject requires a blood draw, fresh tumor biopsy etc., the subject is first required to provide consent to the main study and AEs will be captured according to guidelines for standard AE reporting.

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

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

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

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

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

7.2.2 Reporting of Pregnancy and Lactation to the Sponsor

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

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

Pregnancies and lactations that occur from the time of treatment allocation/randomization through 120 days following cessation of Sponsor's product, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, must be reported by the investigator. All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

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

7.2.3 Immediate Reporting of Adverse Events to the Sponsor

7.2.3.1 Serious Adverse Events

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

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

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

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

Refer to Table 9 for additional details regarding each of the above criteria.

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

For the time period beginning at treatment allocation/randomization through 90 days following cessation of 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 treatment allocation/randomization, any ECI, or follow up to an ECI, that occurs to any subject must be reported within 24 hours to the Sponsor if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

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

Events of clinical interest for this trial include:

1. an overdose of Sponsor's product, as defined in Section 7.2.1 - Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor, that is not associated with clinical symptoms or abnormal laboratory results.

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

   *Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The trial site guidance for assessment

and follow up of these criteria can be found in the Investigator Trial File Binder (or equivalent).

7.2.3.3 Protocol-Specific Exceptions to Serious Adverse Event Reporting

Efficacy endpoints as outlined in this section will not be reported to the Sponsor as described in Section 7.2.3 - Immediate Reporting of Adverse Events to the Sponsor. Any such event will be submitted to the Sponsor within 24 hours either by electronic or paper media.

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

The eDMC 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.

Table 9 Evaluating Adverse Events

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

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

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

7.2.5 Sponsor Responsibility for Reporting Adverse Events

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

7.3 TRIAL GOVERNANCE AND OVERSIGHT

7.3.1 Scientific Advisory Committee

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

7.3.2 Executive Oversight Committee

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

An eDMC recommendation will be communicated to the Sponsor as agreed to in the DMC charter.

Treatment-level results of the study interim analysis will be provided by the external unblinded statistician to the eDMC. The eDMC will review interim trial results, consider overall risk and benefit to trial participants (refer to Section 8.7). The eDMC will make

recommendations to the EOC regarding steps to ensure both subject safety and continued ethical integrity of the trial. Limited additional Sponsor personnel may be unblinded to the treatment level results of the study interim analysis, if required, in order to act on the recommendations of the eDMC or facilitate regulatory filing after the study interim analysis. The extent to which individuals are unblinded with respect to results of study interim analysis will be documented by the unblinded statistician. Additional logistical details, data monitoring guidance and multiplicity adjustment will be provided in the DMC Charter.

8.0 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, 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 the conduct of any analysis, will be documented in a supplemental SAP (sSAP) and referenced in the Clinical Study Report (CSR) for the study. A separate PK analysis plan as well as biomarker analysis plan will be provided. Post hoc exploratory analyses will be clearly identified in the CSR. The PRO analysis plan will also be included in the sSAP.

8.1 Statistical Analysis Plan Summary

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

Statistical Analysis Plan

Study Design Overview	A Phase III, Randomized, Open-label Clinical Trial of Pembrolizumab (MK-3475) versus Paclitaxel in Asian Subjects with Advanced Gastric or Gastroesophageal Junction Adenocarcinoma who Progressed after First-Line Therapy with Platinum and Fluoropyrimidine
Treatment Assignment	Approximately 360 subjects will be randomized in a 1:1 ratio to receive pembrolizumab or paclitaxel. Stratification factors are time to progression (TTP) on first-line therapy (< 6 months vs. ≥ 6 months) and ECOG PS (0 vs. 1). This is an open-label study.
Analysis Populations	Efficacy: Intention to Treat (ITT) Safety: All Subjects as Treated (ASaT)
Primary Endpoints	1. Overall Survival (OS) 2. Progression-free Survival (PFS) per RECIST 1.1 by blinded central radiologists' review
Statistical Methods for Key Efficacy Analyses	The primary hypotheses will be evaluated by comparing pembrolizumab to paclitaxel on PFS per RECIST 1.1 by blinded central radiologists' review and OS 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.

Statistical Methods for Key Safety Analyses	The analysis of safety results will follow a tiered approach. The tiers differ with respect to the analyses that will be performed. There are no Tier 1 events in this trial. 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 analyzed using the Miettinen and Nurminen method [45].
Interim Analysis	No interim analysis for PFS. One interim efficacy analysis planned in this study for OS. Results will be reviewed by an external data monitoring committee. The interim analysis is summarized below. Details are provided in Section 8.7. The interim analysis of OS will be performed at the time of final PFS analysis o Timing: To be performed after: (1) enrollment is completed (2) approximately 235 PFS events and 190 OS events have been observed. o Purpose: final PFS analysis and interim analysis of OS Final analysis (event driven trial) o Timing: at least 290 OS events have been observed, estimated to be 36 months after study start o Purpose: Final analysis of OS
Multiplicity	The overall type I error over the multiple endpoints will be controlled by the Bonferroni procedure, which is strongly controlled at 2.5% (one-sided) with initially 0.35% allocated to PFS and 2.15% allocated to OS hypotheses, and 0% to the ORR hypothesis. If the PFS hypothesis is rejected, the corresponding alpha level can be shifted to the hypotheses for the OS endpoint using the graphical approach of Maurer and Bretz [46]. The secondary hypothesis of ORR will be tested only if pembrolizumab arm is superior to the control in OS.
Sample Size and Power	The planned sample size is approximately 360 subjects. The final analysis of this study is event driven (i.e., follow-up time is subject to change but number of events is not) and will complete after at least 290 OS events have been observed. For the primary endpoint PFS, the trial has >99% (>90%) power to demonstrate that pembrolizumab is superior to paclitaxel at a one-sided 0.35% alpha-level, if the underlying hazard ratio of PFS is 0.5 (0.6). For primary endpoint OS, the trial has 91% power to demonstrate that pembrolizumab is superior to paclitaxel at a one-sided 2.15% alpha-level, if the underlying hazard ratio of OS is 0.67.

8.2 Responsibility for Analyses/In-House Blinding

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

The SPONSOR will generate the randomized allocation schedule(s) for study treatment assignment. The algorithm for the randomized allocation of subjects will be implemented in an interactive voice response system (IVRS).

Although the trial is open label, analyses or summaries generated by randomized treatment assignment, actual treatment received will be limited and documented. In addition, the independent radiologist(s) will perform the blinded central radiologists' review without knowledge of treatment group assignment.

The eDMC will serve as the primary reviewer of the unblinded results of the interim analysis and will make recommendations for discontinuation of the study or protocol modifications to the EOC of this Sponsor. Depending on the recommendation of the eDMC, the Sponsor may prepare a regulatory submission. If the eDMC recommends modifications to the design of the protocol or discontinuation of the study, the EOC may be unblinded to results at the treatment level in order to act on these recommendations.

8.3 Hypotheses/Estimation

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

8.4 Analysis Endpoints

8.4.1 Efficacy Endpoints

Primary

Overall Survival

Overall Survival (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.

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

Progression-free-survival (PFS) is defined as the time from randomization to the first documented disease progression or death due to any cause, whichever occurs first. See Section 8.6.1 for definition of censoring.

Secondary

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

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

8.4.2 Safety Endpoints

Safety measurements are described in Section 7.

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 analyzed according to the correct treatment group and a narrative will be provided for any events that occur during the cycle for which the subject is incorrectly dosed.

At least 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.

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

8.6 Statistical Methods

8.6.1 Statistical Methods for Efficacy Analyses

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

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

8.6.1.1 Overall Survival (OS)

The non-parametric Kaplan-Meier method will be used to estimate the survival curves. The treatment difference in survival will be assessed by the stratified log-rank test. A stratified

Cox proportional hazard model with Efron's method of tie handling will be used to assess the magnitude of the treatment difference (i.e., the hazard ratio). The hazard ratio and its 95% confidence interval from the stratified Cox model with a single treatment covariate will be reported. The stratification factors used for randomization will be applied to both the stratified log-rank test and the stratified Cox model.

Subjects in the paclitaxel arm are expected to discontinue treatment earlier compared to subjects in the pembrolizumab arm, and may switch to another anti PD-1 treatment following the verification of progressive disease by blinded central radiologists' vendor. As an exploratory analysis, the Rank Preserving Structural Failure Time (RPSFT) model proposed by Robins and Tsiatis (1989) [47] may be used to adjust for the effect of crossover to other PD-1 therapies on OS.

Other sensitivity analyses described for the PFS endpoint will be applied to OS endpoint as appropriate. Further details of sensitivity analyses will be described in supplemental SAP.

8.6.1.2 Progression-Free Survival (PFS)

The non-parametric Kaplan-Meier method will be used to estimate the PFS curve in each treatment group. The treatment difference in PFS will be assessed by the stratified log-rank test. A stratified Cox proportional hazard model with Efron's method of tie handling will be used to assess the magnitude of the treatment difference (i.e., 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. The stratification factors used for randomization will be applied to both the stratified log-rank test and the stratified Cox model.

Since disease progression is assessed periodically, progressive disease (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 by blinded central radiologists' review, regardless of discontinuation of study drug. Death is always considered as a confirmed PD event.

In order to evaluate the robustness of the PFS endpoint per 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. If a subject meets multiple criteria for censoring, the censoring criterion that occurs earliest will be applied. The censoring rules for primary and sensitivity analyses are summarized in Table 10.

Table 10 Censoring rules for Primary and Sensitivity Analyses of PFS

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

The proportional hazards assumption on PFS will be examined using both graphical and analytical methods if warranted. The log[-log] of the survival function vs. time for PFS will be plotted for the comparison between pembrolizumab and the paclitaxel arm. If the curves are not parallel, indicating that hazards are not proportional, supportive analyses may be conducted to account for the possible non-proportional hazards effect associated with immunotherapies: for example, using Restricted Mean Survival Time (RMST) method [48], parametric method [49], etc.

One assumption for stratified Cox proportional hazard model is that, the treatment hazard ratio (HR) is constant across the strata. If strong departures from the assumption of the HR being the same for all the strata observed (which can result in a notably biased and/or less powerful analysis), a sensitivity analysis may be performed based on a two-step weighted Cox model approach by Mehrotra 2012 [50], in which the treatment effect is first estimated for each stratum and then the stratum specific estimates are combined for overall inference using sample size weights.

Further details of sensitivity analyses will be described in supplemental SAP.

8.6.1.3 Objective Response Rate (ORR)

Stratified Miettinen and Nurminen's method [45] will be used for comparison of the objective response rates between the treatment arms. The difference in ORR and its 95% confidence interval from the stratified Miettinen and Nurminen's method with strata

weighting by sample size will be reported. The stratification factors used for randomization will be applied to the analysis.

Table 11 summarizes the primary analysis approach for primary and secondary efficacy endpoints. Sensitivity analysis methods are described above for each endpoint.

The strategy to address multiplicity issues with regard to multiple efficacy endpoints and interim analysis is described in Section 8.7, Interim Analyses and in Section 8.8, Multiplicity.

Table 11 Analysis Strategy for Key Efficacy Endpoints

Endpoint/Variable (Description, Time Point)	Statistical Method†	Analysis Population	Missing Data Approach
Primary Hypothesis #1			
OS	Test: Stratified Log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT	Censored at last known alive date
Primary Hypothesis #2			
PFS per RECIST 1.1 by blinded central radiologists' review	Test: 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 are in Table 10.)
ORR per RECIST 1.1 by blinded central radiologists' review	Stratified M & N method‡	ITT	Subjects with missing data are considered non-responders.

† Statistical models are described in further detail in the text. For stratified analyses, the stratification factors used for randomization (time to progression on first-line therapy (< 6 months vs. ≥ 6 months) and ECOG PS (0 vs. 1)), will be applied to the analysis.

‡ Miettinen and Nurminen method.

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.

Tiered Approach

The analysis of safety results will follow a tiered approach (Table 12). The tiers differ with respect to the analyses that will be performed. "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, 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, 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.

For this protocol, there are no Tier 1 events. The broad clinical and laboratory AE categories consisting of the percentage of subjects with any AE, any drug related AE, any Grade 3-5 AE, any serious AE, any AE which is both drug-related and Grade 3-5, any AE which is both serious and drug-related, dose modification due to AE, and who discontinued due to an AE, and death will be considered Tier 2 endpoints. 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.

To properly account for the potential difference in follow-up time between the study arms, which is expected to be longer in the pembrolizumab arm, AE incidence density adjusted for treatment exposure analyses may be performed as appropriate. Based on emerging external data, the supportive analysis strategy for safety parameters may be modified to improve the integrity and efficiency of the design. Should this happen, the change will be documented in supplemental SAP, if not in a protocol amendment, at the earliest time before any unblinding of the data.

Detailed kinetics and characteristics of immune mediated AEs will be summarized in this study.

Table 12 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 Serious AE		X	X
	Any Grade 3-5 AE		X	X
	Any Drug-Related AE		X	X
	Any Serious and Drug-Related AE		X	X
	Any Grade 3-5 and Drug-Related AE		X	X
	Dose Modification due to AE		X	X
	Discontinuation due to AE		X	X
	Death			
	Specific AEs, SOCs, or PDLCs(incidence ≥4 of subjects in one of the treatment groups)		X	X
Tier 3	Specific AEs, SOCs or PDLCs (incidence <4 of subjects in all of the treatment groups)			X
	Change from Baseline Results (Labs, ECGs, Vital Signs)			X

† Adverse Experience references refer to both Clinical and Laboratory AEs.
Note: SOC=System Organ Class; PDLC=Pre-Defined Limit of Change; X = results will be provided.

8.6.3 Summaries of Demographic and Baseline Characteristics

The comparability of the treatment groups for each relevant characteristic will be assessed by the use of tables and/or graphs. No statistical hypothesis tests will be performed on these characteristics. The number and percentage of subjects screened, randomized, the primary reasons for screening failure, and the primary reason for discontinuation will be displayed. Demographic variables (e.g., age), baseline characteristics, primary and secondary diagnoses, and prior and concomitant therapies will be summarized by treatment either by descriptive statistics or categorical tables.

8.7 Interim Analyses

There is no interim efficacy analysis planned in this study for PFS.

There is one interim efficacy analysis planned in this study for OS. For OS, a Hwang-Shih-DeCani alpha-spending function with the gamma parameter (-4) is constructed to implement group sequential boundaries that control the Type-I error rate. The actual boundaries will be determined from the number of OS events observed at the time of the interim analysis, using the alpha-spending function.

The interim OS will be performed at the time of final PFS analysis: (1) enrollment is completed; (2) approximately 235 PFS events and 190 OS events have been observed. The

final analysis (FA) for OS will be performed when at least 290 OS events have been observed (~36 months after trial starts).

The secondary hypothesis of ORR will be tested only if pembrolizumab arm is superior to the control in OS. The information fraction for the group sequential boundaries and alpha spending function of ORR will be defined by the proportion of subjects whose randomization dates are at least 6 months before the data cutoff date of the analysis. Only these eligible subjects can be included into the ORR analysis. It is projected that there will be at least 270 eligible subjects at the interim analysis time point. The nominal Type I error rates for the interim analysis and final analysis that will allow tight control of the overall Type I error for testing the ORR hypothesis will be derived using the alpha-spending function approach. The group sequential testing of the ORR hypothesis will be conducted with an efficacy boundary only. The efficacy boundary for the ORR will be set using an Exponential spending function $f(t) = \alpha^{t^{-\nu}}$ [51] with parameter ν=0.25, which yields a Pocock-like boundary.

Table 13 summarizes the timing, number of events and decision guidance for the PFS, OS and ORR analysis. The actual boundaries and the alpha level for the OS and ORR analyses will be determined from the actual number of events observed at the time of the analysis using the corresponding alpha-spending function.

Table 13 Summary of Timing, Sample Size and Decision Guidance of Interim Analysis and Final analysis

Analysis	Criteria for Conduct of Analysis	Endpoint	p value (1-sided) at boundary	Approx. Observed HR or ORR-Difference at Boundary
Final PFS Analysis/ Interim OS Analysis	~ 24 months after trial starts (1) enrollment is complete (2) approximately 235 PFS events and 190 OS events have been observed PFS Events: ~235 OS Events: ~190	PFS	0.0035	0.70
		OS	0.0051	0.69
		ORR†	0.0161	10.2%
Final OS Analysis	~ 36 mos after trial starts At least 290 OS events have been observed OS Events: ~290	OS	0.0198	0.78
		ORR†	0.0123	9.3%

†: The secondary hypothesis of ORR will be tested only if pembrolizumab arm is superior to the control in OS. The assumed expected ORR in pembrolizumab and control groups are 30% and 10%, respectively. Depending on the results of the OS and PFS hypothesis testing, the ORR hypothesis can be tested at Type I error levels of α=2.15% or 2.5%; this table assumes an ORR Type I error of 2.15%.

The eDMC will conduct interim safety analyses approximately every 6 months during the trial. For the situation in which the eDMC requests efficacy information to evaluate risk and benefit during interim safety analyses, additional details regarding the control of Type I error rates for the interim efficacy analysis will be provided in the DMC Charter.

8.8 Multiplicity

The multiplicity strategy specified in this section will be applied to the two primary hypotheses (superiority of pembrolizumab on OS or PFS) and one secondary hypothesis (superiority of pembrolizumab on ORR).

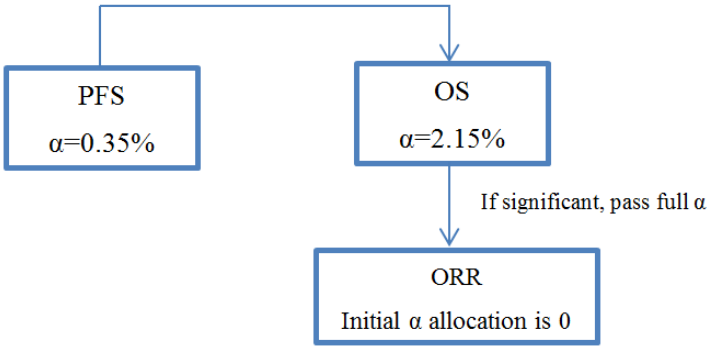
The overall Type-I error is strongly controlled at 2.5% (one-sided), with 0.35% allocated to PFS and 2.15% allocated to OS hypothesis and 0% to the ORR hypothesis.

For the OS and ORR endpoints, the Type-I error rate for the interim analysis and final analysis is controlled through alpha-spending functions as described in Section 8.7, Interim Analyses.

By using the graphical approach of Maurer and Bretz [46], if the PFS hypothesis is rejected, the corresponding alpha level can be shifted to the OS hypotheses. If the OS hypothesis is rejected, the corresponding alpha level can be shifted to the ORR.

See Figure 3 for the multiplicity strategy diagram of the study.

Figure 3 Multiplicity Strategy



8.9 Sample Size and Power Calculations

The study will randomize subjects in a 1:1 ratio into pembrolizumab arm and paclitaxel arm. The overall sample size will be approximately 360. However, subjects already in screening phase may be enrolled even after we have reached the maximum sample size.

The final analysis of the study is event driven (i.e., follow-up time are subject to change but number of events is not) and will complete after at least 290 OS events have been observed.

PFS analysis: the final PFS analysis will be performed after approximately 235 PFS events observed. With ~235 PFS events, this trial has overall 99% (88%) power to demonstrate that pembrolizumab is superior to paclitaxel at a one-sided 0.35% alpha-level, if the underlying hazard ratio of PFS is 0.5 (0.6). Success for PFS at the main analysis approximately corresponds to an observed hazard ratio of < 0.70.

The power calculation is based on the following assumptions for subjects: 1) Progression-free survival follows an exponential distribution with a median of 4.5 months in the paclitaxel arm; 2) An enrollment period of 24 months (IA is conducted after enrollment is complete); 3) A yearly drop-out rate of 5%.

OS analysis: The final OS analysis will be carried out when at least 290 OS events have occurred. For primary endpoint OS, the trial has 91% (85%) power to demonstrate that pembrolizumab is superior to paclitaxel at an one-sided 2.15% alpha-level, if the underlying hazard ratio of OS is 0.67 (0.7). Success for OS at the final analysis approximately corresponds to an observed hazard ratio of < 0.78 (approximately a 2-month improvement or greater in median OS).

The sample size and power calculation is based on the following assumptions for subjects: 1) Overall survival follows an exponential distribution with a median of 7.5 months in the control arm; 2) An enrollment period of 24 months and a minimum of 12 months follow-up after enrollment completion; 3) A yearly dropout rate of 2%.

The assumptions for the median PFS of 4.5 months and the median OS of 7.5 months in the paclitaxel arm are based on estimates of median PFS and median OS from China subgroup analysis of TyTAN trial [40].

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 dual primary endpoints will be estimated and plotted within each category of the following classification variables:

- Age category (≤65 vs. >65 years)
- Sex (Female vs. Male)
- ECOG Performance Scale (0 vs. 1)
- Primary location (Stomach vs. GEJ)
- Histological subtype (Diffuse vs. intestinal vs. mixed)
- Disease Status (Locally advanced vs. Metastatic)
- Time to progression on first-line therapy (< 6 months vs. ≥ 6 months)
- Geographic region of enrolling site (China vs. ex-China)

Country specific population (e.g. Chinese, etc.) may also be analyzed per local regulatory requirements.

8.11 Compliance (Medication Adherence)

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

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 14.

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 14 Product Descriptions

Product Name & Potency	Dosage Form	Source/Additional Information
Pembrolizumab (MK-3475), 25 mg/mL	IV Infusion	Provided centrally by the Sponsor
Paclitaxel, 6 mg/mL	IV Infusion	Provided centrally by the Sponsor or locally by the trial site, subsidiary, or designee

All supplies indicated in Table 14 will be provided per the "Source/Additional Information" column depending on local country operational requirements.

Any commercially available product not included in Table 14 will be provided by the trial site, subsidiary or designee. Every attempt should be made to source these supplies from a single lot/batch number. The trial site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product as per local guidelines unless otherwise instructed by the Sponsor.

9.2 Packaging and Labeling Information

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

Subjects will receive open label pembrolizumab (MK-3475) vials or paclitaxel kits as described in this protocol. Each paclitaxel kit box will contain one commercial vial.

9.3 Clinical Supplies Disclosure

This trial is open-label; therefore, the subject, the trial site personnel, the Sponsor and/or designee are not blinded. Study drug identification (name, strength or potency) is included in the label text; random code/disclosure envelopes or lists are not provided.

9.4 Storage and Handling Requirements

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

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

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

9.5 Discard/Destruction/Returns and Reconciliation

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

9.6 Standard Policies

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

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

10.1 Confidentiality

10.1.1 Confidentiality of Data

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

except to the extent that it is included in a publication as provided in the Publications section of this protocol.

10.1.2 Confidentiality of Subject Records

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

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

10.1.3 Confidentiality of Investigator Information

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

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

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

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

10.1.4 Confidentiality of IRB/IEC Information

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

10.2 Compliance with Financial Disclosure Requirements

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

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

10.3 Compliance with Law, Audit and Debarment

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

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

The investigator also agrees to allow monitoring, audits, IRB/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 Protocol/CSR CI during the anticipated review process, thorough understanding of clinical trial methods, appropriate enrollment of subject cohort, timely achievement of trial milestones). The Protocol CI must be a participating trial investigator.

10.4 Compliance with Trial Registration and Results Posting Requirements

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

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

10.5 Quality Management System

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

10.6 Data Management

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

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

10.7 Publications

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

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

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

Authorship credit should be based on 1) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; and 3) final approval of the version to be published. Authors must meet conditions 1, 2 and 3. Significant contributions to trial execution may also be taken into account to determine authorship, provided that contributions have also been made to all three of the preceding authorship criteria. Although publication planning may begin before conducting the trial, final decisions on authorship and

the order of authors' names will be made based on participation and actual contributions to the trial and writing, as discussed above. The first author is responsible for defending the integrity of the data, method(s) of data analysis and the scientific content of the manuscript.

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

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12.0 APPENDICES

12.1 Merck Code of Conduct for Clinical Trials

Merck*
Code of Conduct for Clinical Trials

I. Introduction

A. Purpose

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

B. Scope

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

II. Scientific Issues

A. Trial Conduct

1. Trial Design

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

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

2. Site Selection

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

3. Site Monitoring/Scientific Integrity

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

B. Publication and Authorship

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

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

III. Subject Protection

A. IRB/ERC review

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

B. Safety

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

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

C. Confidentiality

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

D. Genomic Research

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

IV. Financial Considerations

A. Payments to Investigators

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

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

B. Clinical Research Funding

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

C. Funding for Travel and Other Requests

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

V. Investigator Commitment

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

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

12.2 Collection and Management of Specimens for Future Biomedical Research

1. Definitions

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

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

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

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research

The specimens consented and/or collected in this trial as outlined in Section 7.1.3.3 – Future Biomedical Research Samples will be used in various experiments to understand:

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

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

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

3. Summary of Procedures for Future Biomedical Research

a. Subjects for Enrollment

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

b. Informed Consent

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

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

c. eCRF Documentation for Future Biomedical Research Specimens

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

d. Future Biomedical Research Specimen(s)

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

4. Confidential Subject Information for Future Biomedical Research

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

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

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

5. Biorepository Specimen Usage

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

6. Withdrawal From Future Biomedical Research

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

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

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

7. Retention of Specimens

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

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

8. Data Security

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

9. Reporting of Future Biomedical Research Data to Subjects

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

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

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

10. Future Biomedical Research Study Population

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

11. Risks Versus Benefits of Future Biomedical Research

For 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 (i.e., only remainder of 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.

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

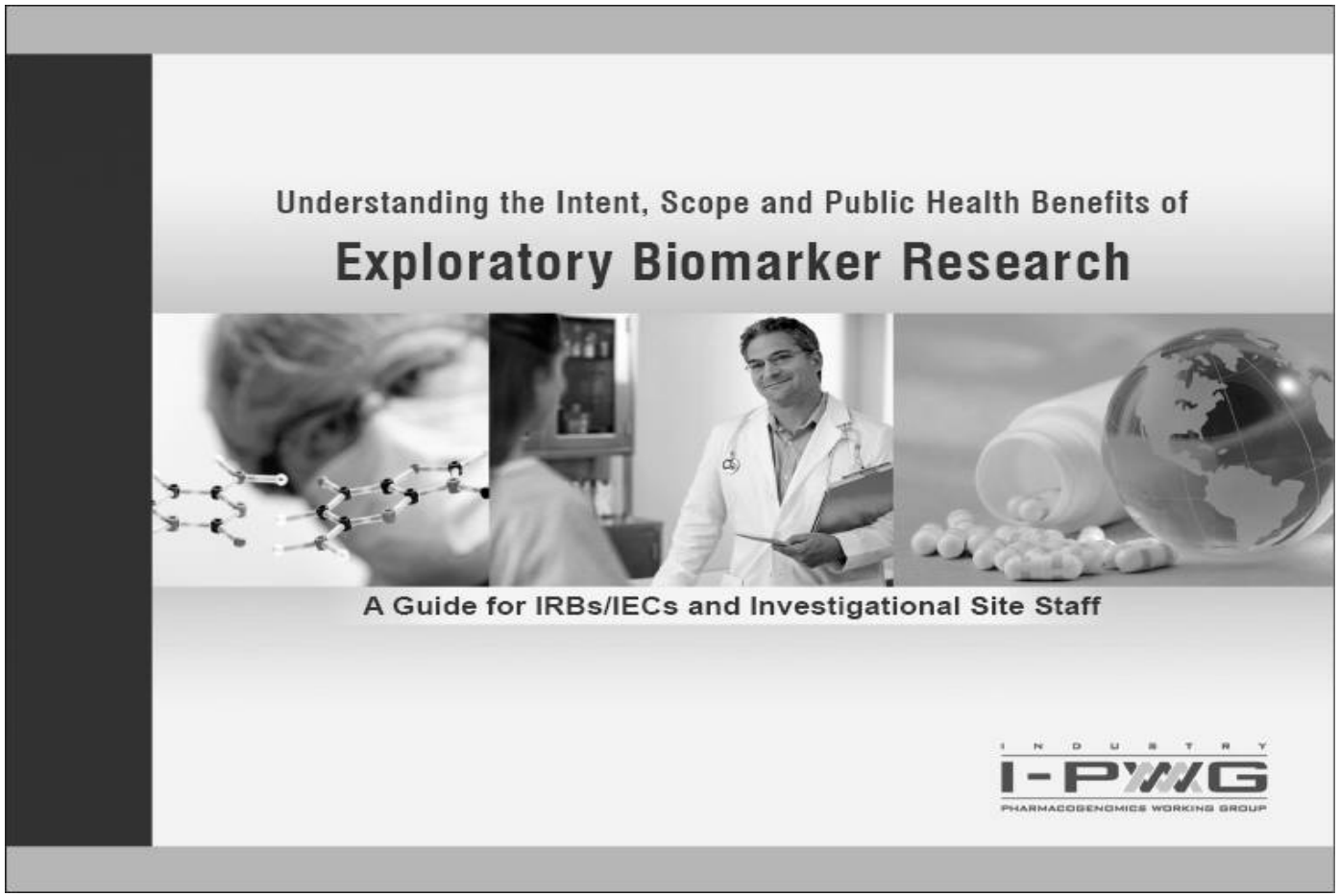
12. Questions

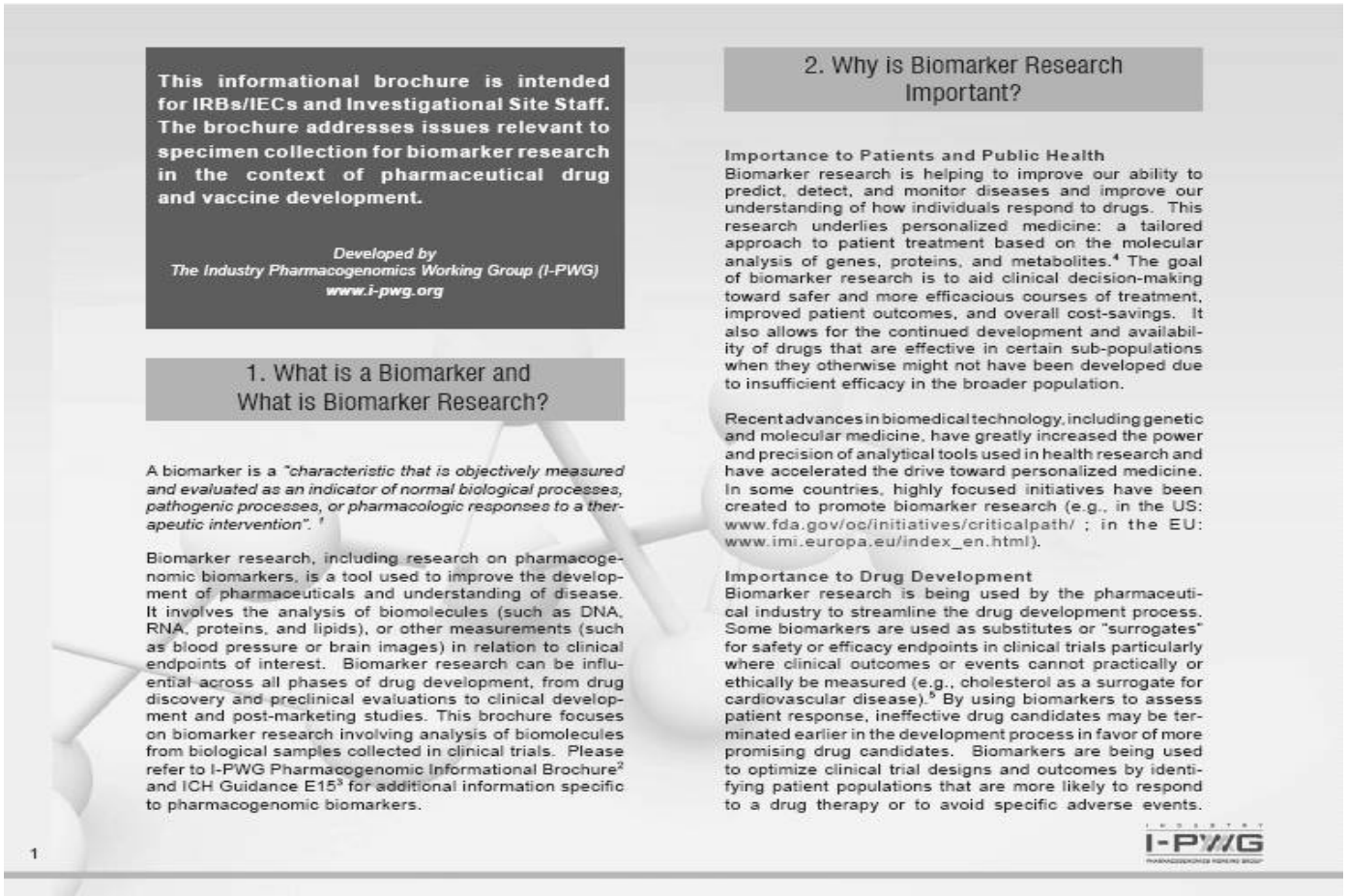
Any questions related to the future biomedical research should be e-mailed directly to clinical.specimen.management@merck.com.

13. References

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

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





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

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

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

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

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

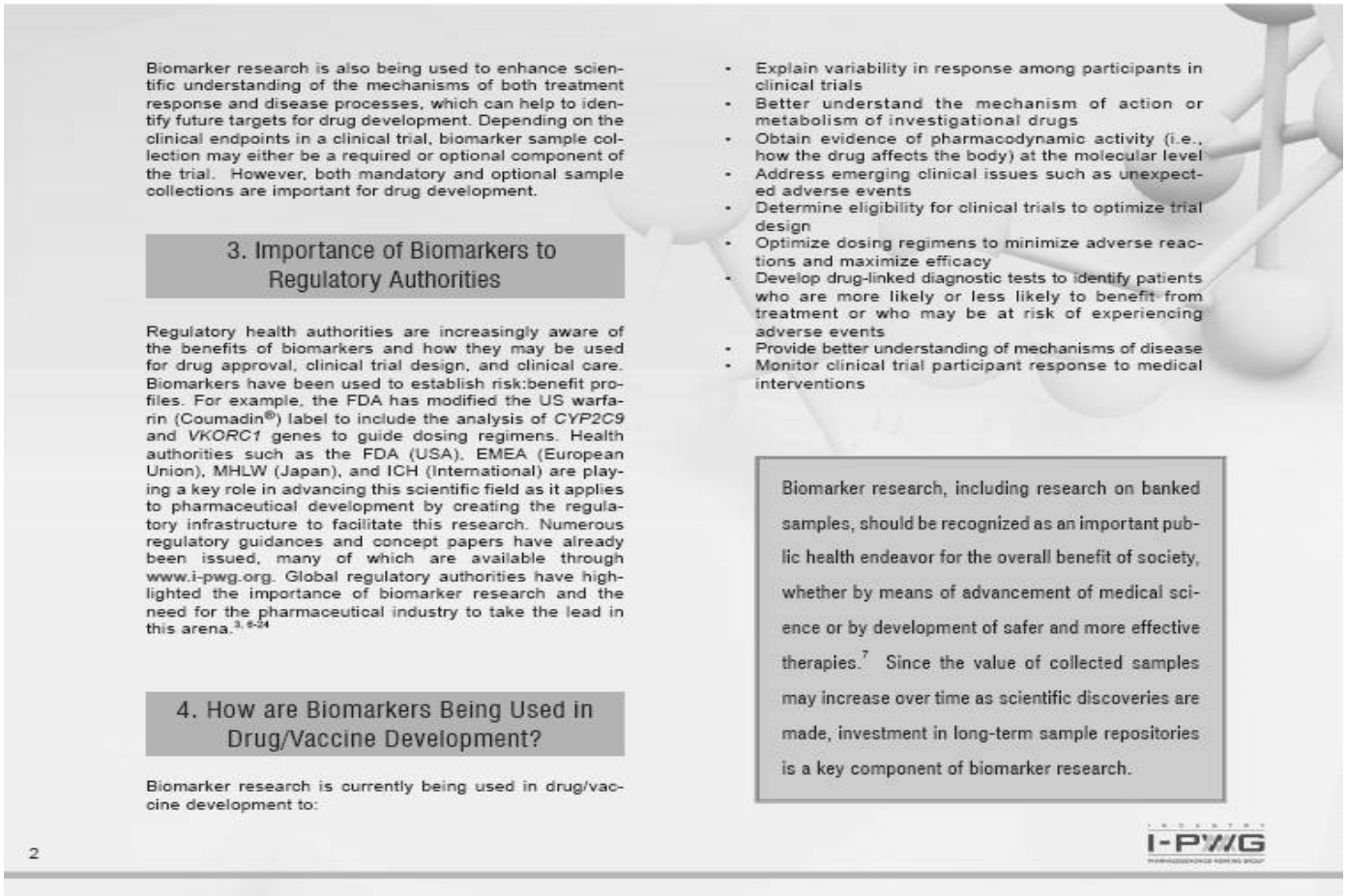
2. Why is Biomarker Research Important?

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

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

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

1


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.
2
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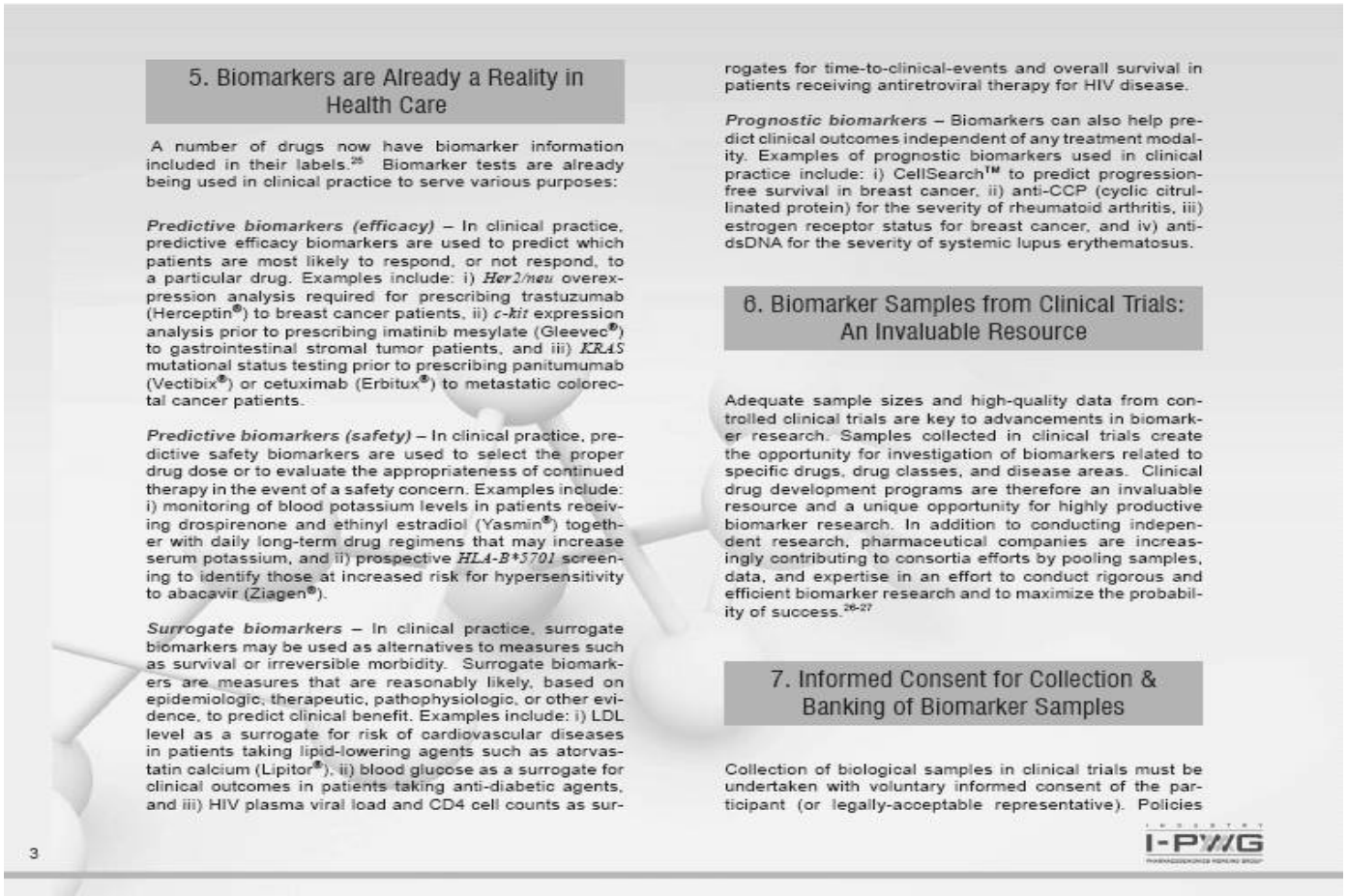

5. Biomarkers are Already a Reality in Health Care

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

3

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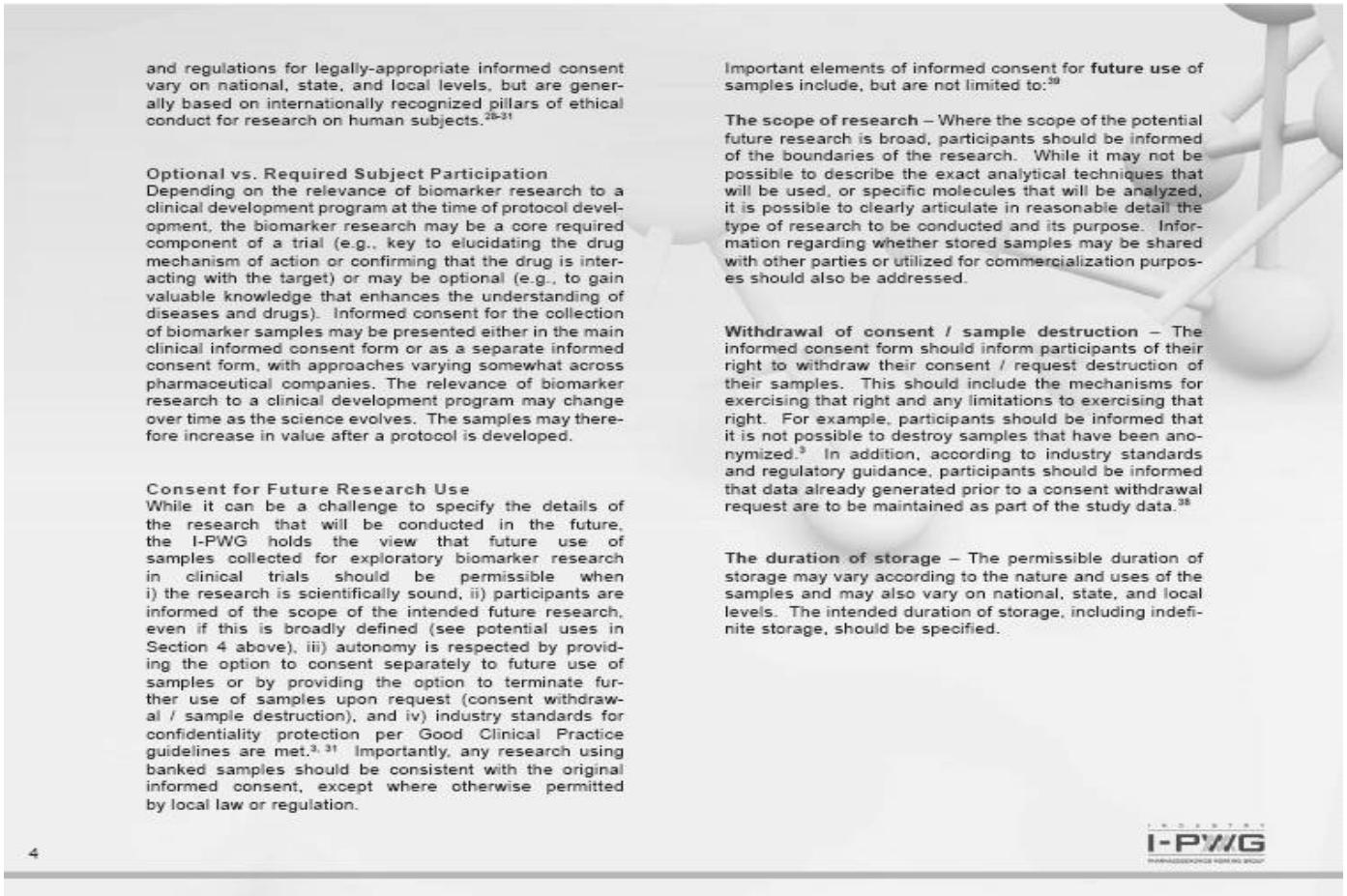

and regulations for legally-appropriate informed consent vary on national, state, and local levels, but are generally based on internationally recognized pillars of ethical conduct for research on human subjects.[28-31]

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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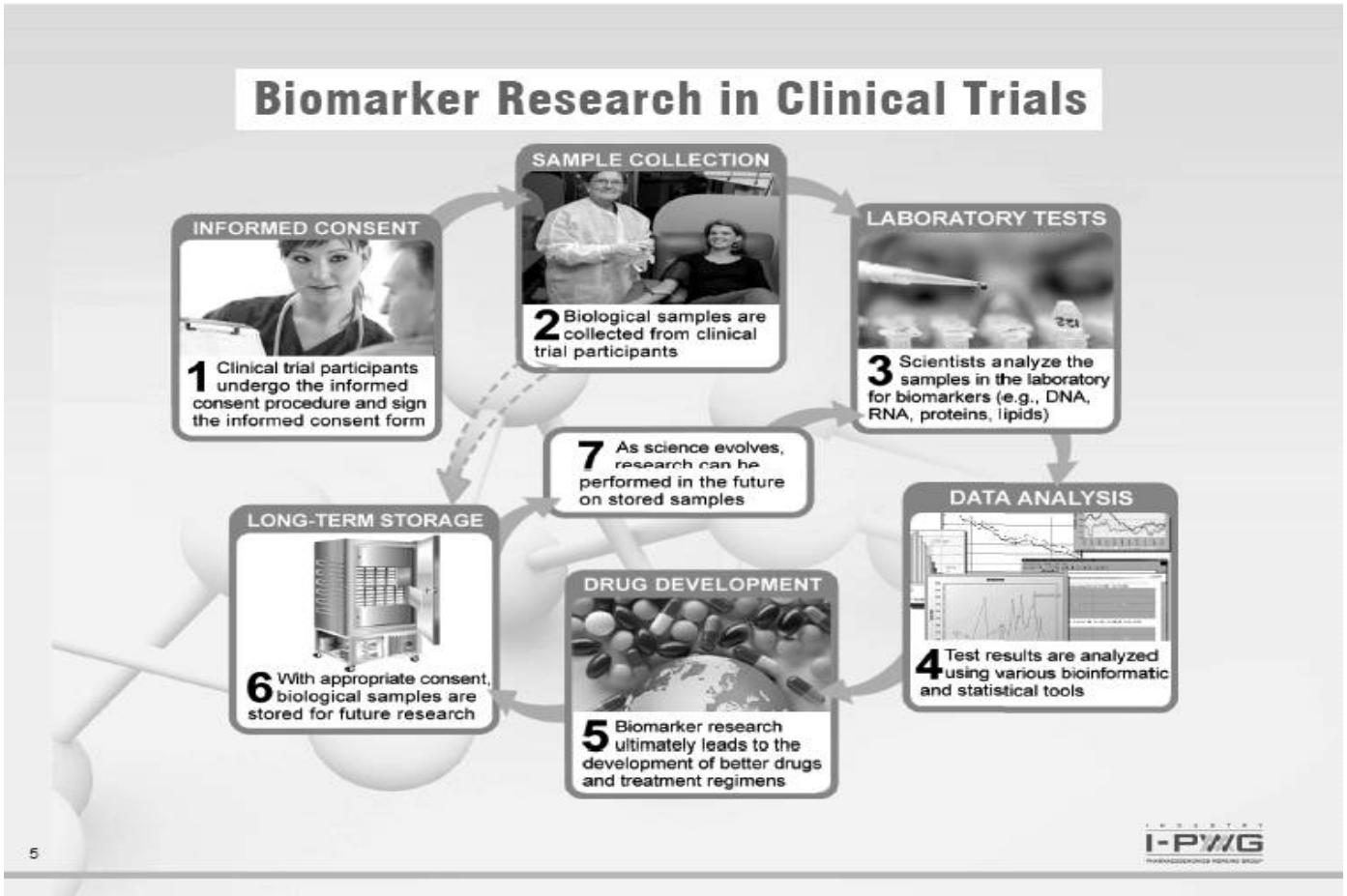
Biomarker Research in Clinical Trials
SAMPLE COLLECTION
2 Biological samples are collected from clinical trial participants
LABORATORY TESTS
3 Scientists analyze the samples in the laboratory for biomarkers (e.g., DNA, RNA, proteins, lipids)
INFORMED CONSENT
1 Clinical trial participants undergo the 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
5
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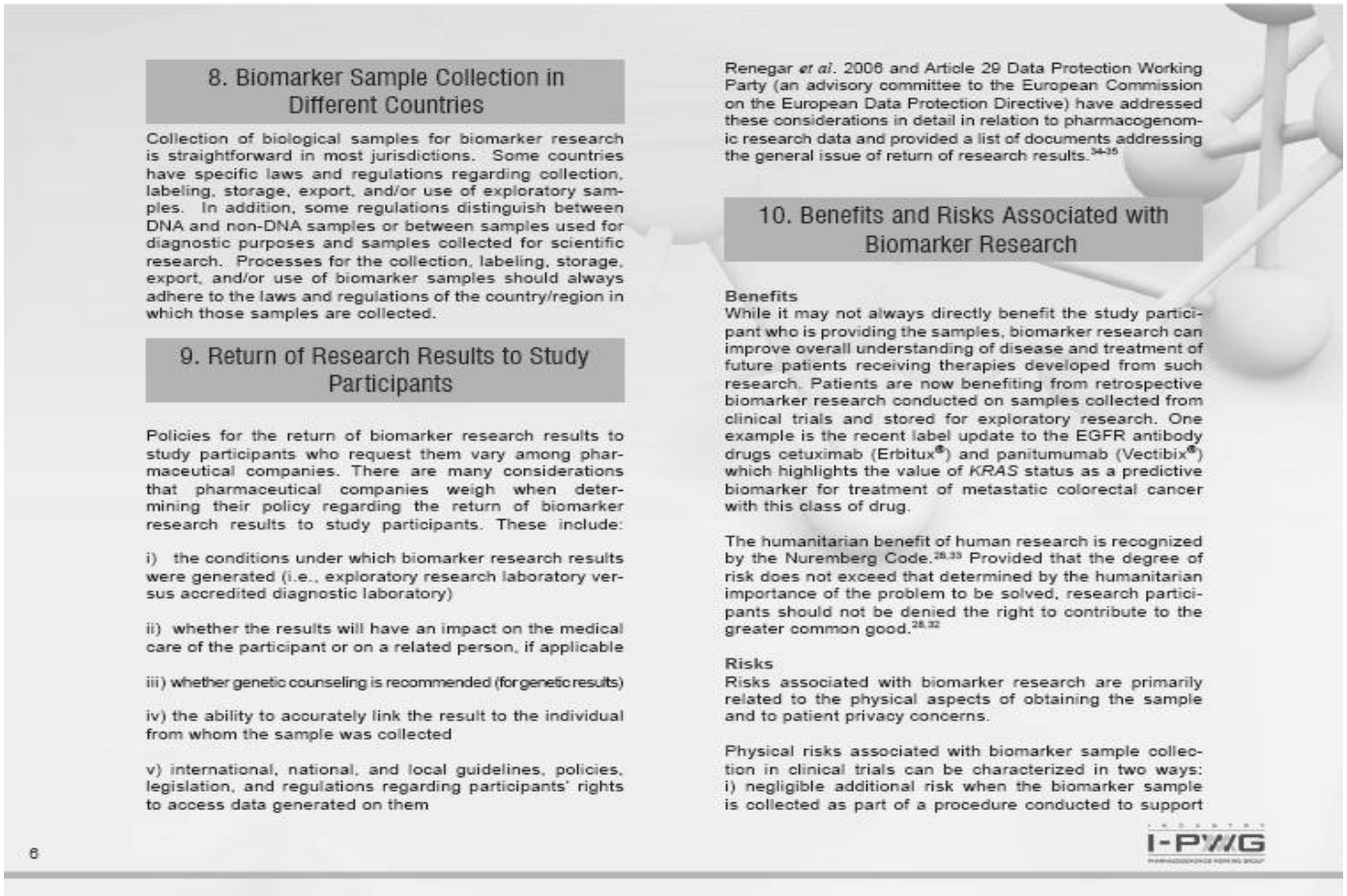

8. Biomarker Sample Collection in Different Countries

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

9. Return of Research Results to Study Participants

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

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

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

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

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

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

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

10. Benefits and Risks Associated with Biomarker Research

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

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

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

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

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

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

11. Privacy, Confidentiality, and Patient Rights

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

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

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

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

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

12.Where to Get More Information?

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

13. What is I-PWG?

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

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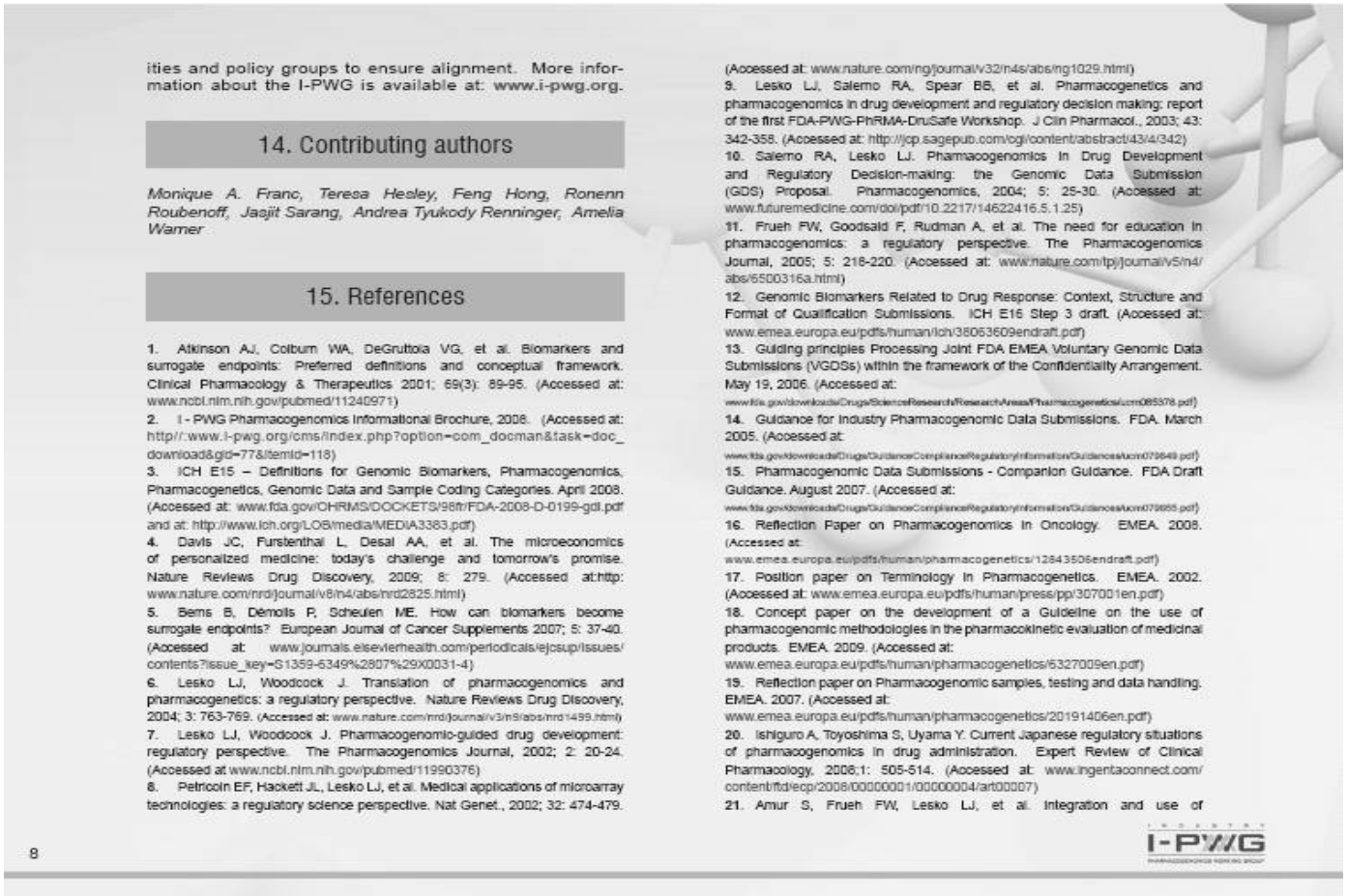

ities and policy groups to ensure alignment. More information about the I-PWG is available at: www.i-pwg.org.

14. Contributing authors

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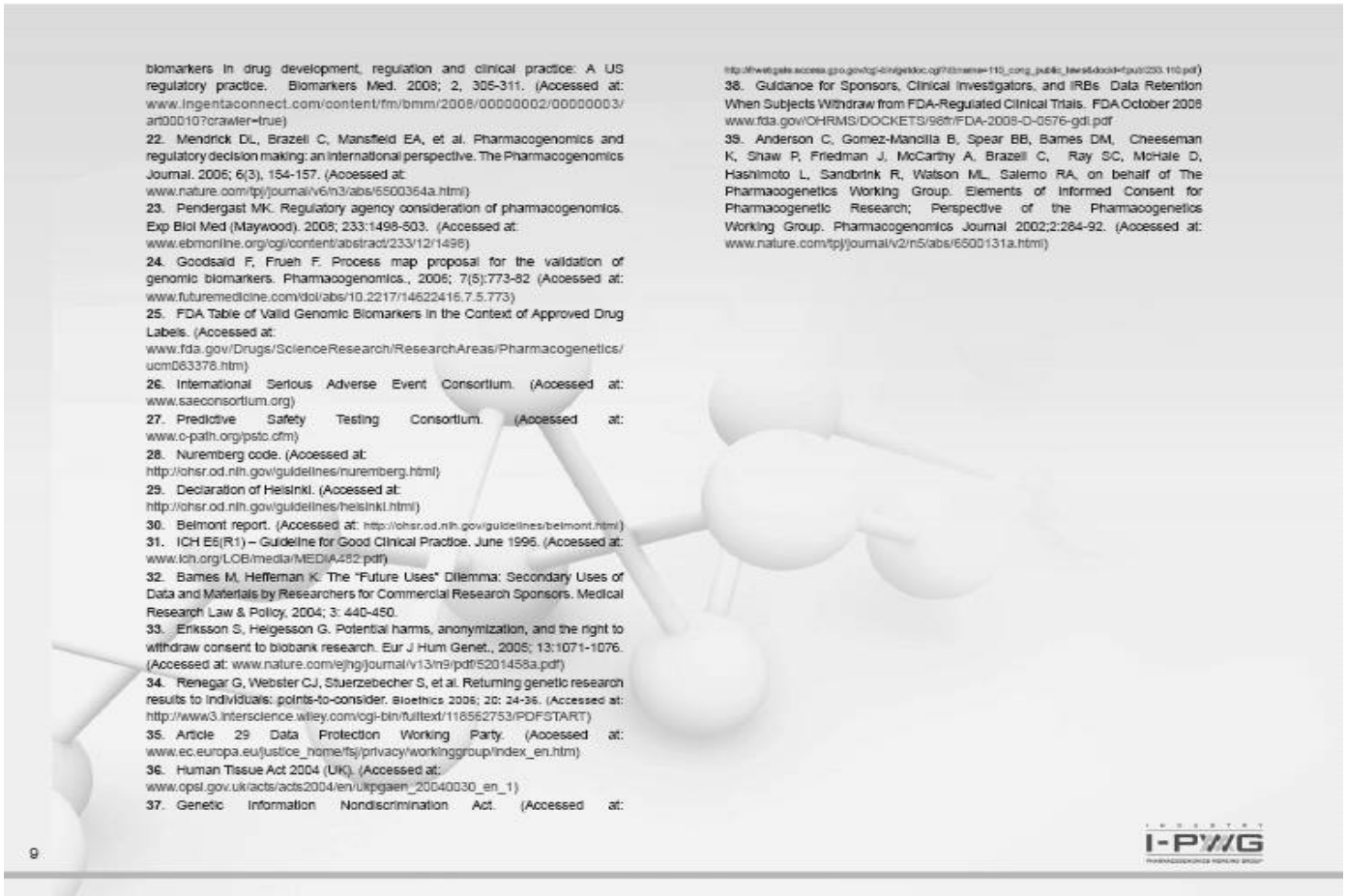

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12.4 ECOG Performance Status

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, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

* 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 adverse event reporting. (http://ctep.cancer.gov/reporting/ctc.html).

12.6 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
APaT	All Patients 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
β-HCG	Beta Human Chorionic Gonadotropin
BSA	Body Surface Area
CBC	Complete Blood Count
CD	Cluster of Differentiation
CI	Confidence Interval
CNS	Central Nervous System
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
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 Organisation for Research and Treatment of Cancer

Abbreviation/Term	Definition
ERC	Ethics Review Committee
FBR	Future Biomedical Research
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FDAMA	Food and Drug Administration Modernization Act
FNA	Fine Needle Aspirate
GCP	Good Clinical Practice
GEJ	Gastroesophageal Junction
FP	Cisplatin + 5- FU
5-FU	5-fluoruracil
GFR	Glomerular Filtration Rate
HBsAg	Hepatitis B surface Antigen
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HNSCC	Head and Neck Squamous Cell Carcinoma
HPV	Human Papillomavirus
HRQoL	Health Related Quality of Life
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
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
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.

Abbreviation/Term	Definition
NA or N/A	Not Applicable
NCI	National Cancer Institute
NSAID	Non-Steroidal Anti-inflammatory Drug
NSCLC	Non-Small Cell Lung Cancer
ORR	Objective Response Rate
OS	Overall Survival
OTC	Over-the-counter
PD	Progressive Disease
PD-1	Programmed cell death 1
PD-L1	Programmed death-ligand 1
PD-L2	Programmed death-ligand 2
PFS	Progression-Free Survival
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
SAE	Serious Adverse Events
SAP	Statistical Analysis Plan
SFU	Survival Follow-Up
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
siDMC	Standing Internal Data Monitoring Committee
SOP	Standard Operating Procedures
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 – TRIAL PROCEDURES (Assessing and Recording Adverse Events). I also agree to handle all clinical supplies provided by the Sponsor and collect and handle all clinical specimens in accordance with the protocol. I understand that information that identifies me will be used and disclosed as described in the protocol, and that such information may be transferred to countries that do not have laws protecting such information. Since the information in this protocol and the referenced Investigator's Brochure is confidential, I understand that its disclosure to any third parties, other than those involved in approval, supervision, or conduct of the trial is prohibited. I will ensure that the necessary precautions are taken to protect such information from loss, inadvertent disclosure or access by third parties.

TYPED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	