Official Protocol Title:	A Phase III, Randomized, Open-label Clinical Trial of Pembrolizumab (MK-3475) versus Paclitaxel in Subjects with Advanced Gastric or Gastroesophageal Junction Adenocarcinoma who Progressed after First-Line Therapy with Platinum and Fluoropyrimidine
NCT number:	NCT02370498
Document Date:	09-Mar-2020

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TITLE:

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

IND NUMBER: 123,482
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DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
3475-061-13 (Global Amendment)	09-MAR-2020	To include an extension study.
3475-061-12 (UK-Specific Amendment)	28-NOV-2017	To clarify language in alignment with the labels – USPI and SmPC and the core data sheet and to add guidelines for the management of myocarditis to the table based upon health authority feedback. To allow flexibility in the entire follow-up period beyond just the current survival follow-up portion to enable more frequent follow-ups as necessary.
3475-061-11 (Global Amendment)	03-NOV-2017	To clarify language in alignment with the labels – USPI and SmPC and the core data sheet and to add guidelines for the management of myocarditis to the table based upon health authority feedback. To allow flexibility in the entire follow-up period beyond just the current survival follow-up portion to enable more frequent follow-ups as necessary.
3475-061-10 (UK-Specific Amendment)	13-SEP-2017	The timing was updated to allow for adequate follow-up time before the final analysis in order to account for a potential delayed treatment effect on overall survival.

Document	Date of Issue	Overall Rationale
3475-061-09 (Global Amendment)	25-AUG-2017	The timing was updated to allow for adequate follow-up time before the final analysis in order to account for a potential delayed treatment effect on overall survival.
3475-061-08 (UK-Specific Amendment)	29-AUG-2016	The revisions were based on the recommendations from the external Data Monitoring Committee to no longer enroll PD-L1 negative participants as of 20-MAR-2016.
3475-061-07 (Global Amendment)	18-AUG-2016	The revisions were based on the recommendations from the external Data Monitoring Committee to no longer enroll PD-L1 negative participants as of 20-MAR-2016.
3475-061-06 (UK-Specific Amendment)	21-DEC-2015	Due to the higher than anticipated prevalence rate for PD-L1+ patients, the interim futility analysis for PD-L1patientsis no longer necessary.
3475-061-05 (Global Amendment)	23-NOV-2015	Due to the higher than anticipated prevalence rate for PD-L1+ patients, the interim futility analysis for PD-L1patientsis no longer necessary.

Document	Date of Issue	Overall Rationale
3475-061-04 (UK-Specific Amendment)	10-JUN-2015	Enable to better monitor disease response and progression based on evolving gastric cancer studies. Additionally, increasing the imaging interval after median progression may artificially lengthen the progression time in a substantial number of patients. Disease stratification factors (time to progression on first-line therapy and PD-L1 expression status) may help predict response in second-line gastric cancer treatment and consequently overall survival in gastric cancer patients.
3475-061-03 (UK-Specific Amendment)	01-MAY-2015	To align with country-specific local regulations regarding pregnancy testing in UK.
3475-061-02 (Global Amendment)	05-MAY-2015	Enable to better monitor disease response and progression based on evolving gastric cancer studies. Additionally, increasing the imaging interval after median progression may artificially lengthen the progression time in a substantial number of patients. Disease stratification factors (time to progression on first-line therapy and PD-L1 expression status) may help predict response in second-line gastric cancer treatment and consequently overall survival in gastric cancer patients.
3475-061-00	15-JAN-2015	Original

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: Pembrolizumab Extension Study.	
5.10	Beginning and End of the Trial	Added: Upon study completion, participants will be discontinued and **may be** enrolled in a pembrolizumab extension study.	

ADDITIONAL CHANGE(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
7.1.1.8	Trial Compliance (Medication/Diet/Activity/Other)	Changed the word "witnessed" to "monitored"	To describe appropriately the work being done by the investigator and/or trial staff.
7.1.2.6.3 (Added)	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 iCRO for quality control, storage, and possible retrospective review.	To clarify tumor imaging procedures during Second Course Phase.

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
		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.	

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
7.1.2.6.4	Assessment of Disease	Originally Section 7.1.2.6.3 but moved to 7.1.2.6.4. Therefore, all references to Assessment of Disease was updated to 7.1.2.6.4.	Due to the addition of Second Course (Retreatment) Tumor Imaging (Section 7.1.2.6.3), Assessment of Disease was moved to Section 7.1.2.6.4.
6.3	Second Course Phase (Retreatment with Pembrolizumab)	Footnote m: Added "See Section 7.1.2.6.3."	
4.2.3.4	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.
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.	

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

1.0 TRIAL SUMMARY

Abbreviated Title	Pembrolizumab (MK-3475) vs Paclitaxel in 2L Participants with Advanced Gastric Adenocarcinoma
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 up to 720 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 visit.
Duration of Participation	Each participant will participate in the trial from the time the participant signs the informed consent form (ICF) through the final contact. After a screening phase of up to 28 days, eligible participants 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) (AEs), intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw the participant, participant withdraws consent, pregnancy of the participant, noncompliance with trial treatment or procedure requirements, participant receives 35 administrations (approximately 2 years) of pembrolizumab, or administrative reasons requiring cessation of treatment. After the end of treatment, each participant will be followed for 30 days for AE monitoring (serious adverse events and events of clinical interest will be collected for 90 days after the end of treatment or 30 days after the end of treatment if the participant initiates new anticancer therapy, whichever is earlier).

	Participants 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 complete response may be eligible for up to one year of retreatment after they have experienced radiographic disease progression. Participants 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 participants 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, multicenter, open-label trial of pembrolizumab (MK-3475) versus paclitaxel in participants with advanced gastric or GEJ adenocarcinoma who have progressed after failure of any combination chemotherapy containing a platinum and a fluoropyrimidine agent.

In this trial, up to approximately 720 participants will be randomized to compare the efficacy and safety of pembrolizumab versus paclitaxel. Participants will be randomized in a 1:1 ratio to receive pembrolizumab or paclitaxel and stratified by geographic region, time to progression on first-line therapy, and programmed cell death ligand 1 (PD-L1) expression status.

Based on recommendations from an external Data Monitoring Committee, PD-L1 negative participants are no longer eligible for enrollment into the study as of 20-MAR-2016; however, all participants enrolled prior to 20-MAR-2016 may continue on the study regardless of PD-L1 status. Therefore, as of 20-MAR-2016, enrollment will only include those participants with PD-L1 positive expressions on their tumor. This enrollment change does not impact the Statistical Analysis Plan. Enrollment was completed on 27-JUL-2016.

Participants will be required to provide tissue of a tumor lesion to be evaluated at a central laboratory for expression status of PD-L1. An evaluable specimen for PD-L1 status must be available and confirmed prior to enrollment. As of 20-MAR-2016, a PD-L1 positive result must be confirmed prior to enrollment.

The overall study enrollment will be driven by the number of participants with PD-L1 positive expression on their tumor (n = 360). That is, enrollment will stop when approximately 360 participants with PD-L1 positive expression on their tumor have been randomized. Additionally, there will be a cap on enrollment (approximately 30% of total) for randomized participants residing in the Asia Pacific region for this study.

All study participants 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 progression free survival (PFS) and overall survival (OS). The primary PFS analysis will be based on Response Evaluation Criteria In Solid Tumors Version 1.1 (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 has been modified as described in Section 7.1.2.6.4.1 to allow for continued treatment and a repeat confirmatory scan in participants with initial evidence of progressive disease (PD) by standard RECIST 1.1 (hereafter referred to as immune-related RECIST [irRECIST]). If a participant has progression of disease by RECIST 1.1, it is recommended that the participant be discontinued from the study treatment unless, in the investigator's opinion, the participant is deriving benefit from treatment. Clinically stable participants, as defined in Section 7.1.2.6.4.1, may continue to receive trial therapy at the discretion of the investigator. If a

repeat scan confirms progression of disease and the participant remains clinically stable, the participant may continue treatment after consultation with the Sponsor.

AEs will be monitored throughout the trial and graded in severity according to the guidelines outlined in the National Cancer Institute's (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 AEs, intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw the participant, participant withdraws consent, pregnancy of the participant, noncompliance with trial treatment or procedure requirements, completion of 35 administrations (approximately 2 years) of pembrolizumab, or administrative reasons requiring the cessation of treatment.

Participants 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. Participants 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 re-treat will be at the discretion of the investigator only if no cancer treatment was administered since the last dose of pembrolizumab, the participant 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). Participants within the paclitaxel arm will continue on treatment until disease progression or unacceptable toxicity. A crossover of treatment groups after documented disease progression on the study treatment will not be allowed.

After the end of treatment, each participant will be followed for 30 days for AE monitoring (serious adverse events [SAEs] and events of clinical interest [ECIs] will be collected for 90 days after the end of treatment or 30 days after the end of treatment if the participant initiates new anticancer therapy, whichever is earlier). Participants 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 participants will be followed by telephone contact for OS 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 adaptive design based on pre-specified criteria, using 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 is one planned interim analysis (IA). For further details, please refer to Section 8 of the protocol.

2.2 Trial Diagram

The trial design is depicted in Figure 1.

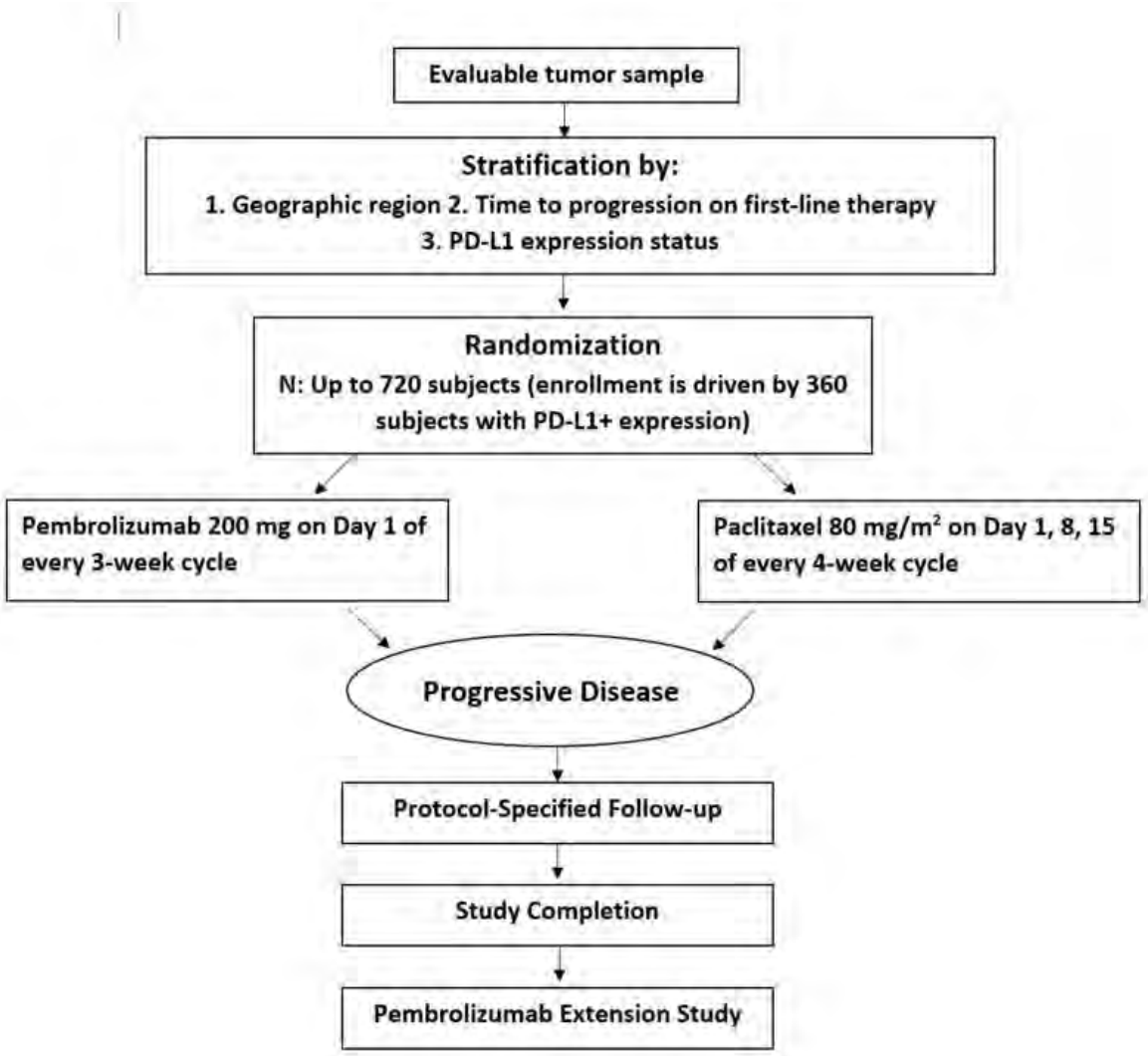


Figure 1 Trial Design Schematic

3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

3.1 Primary Objective(s) & Hypothesis(es)

(1) **Objective**: To evaluate PFS per RECIST 1.1 by blinded central radiologists' review of participants with PD-L1 positive expression with advanced gastric or GEJ adenocarcinoma who have progressed on one previous line of therapy, when treated with pembrolizumab compared to paclitaxel.

Hypothesis: Pembrolizumab prolongs PFS per RECIST 1.1 by blinded central radiologists' review of participants with PD-L1 positive expression (with advanced gastric or GEJ adenocarcinoma who have progressed on 1 previous line of therapy), compared to paclitaxel.

(2) **Objective**: To evaluate OS of participants with PD-L1 positive expression with advanced gastric or GEJ adenocarcinoma who have progressed on one previous line of therapy, when treated with pembrolizumab compared to paclitaxel.

Hypothesis: Pembrolizumab prolongs OS of participants with PD-L1 positive expression (with advanced gastric or GEJ adenocarcinoma who have progressed on 1 previous line of therapy), compared to paclitaxel.

The study is considered to have met its primary objective in the primary population of participants with positive PD-L1 expression if pembrolizumab is superior to paclitaxel either in PFS or in OS at IA or the final analysis (FA).

3.2 Secondary Objective(s) & Hypothesis(es)

If either endpoint (PFS or OS) is successful in the participants with positive PD-L1 expression, the trial is successful for that endpoint in the all participants if pembrolizumab is superior to paclitaxel in the all participants.

(1) **Objective:** To evaluate PFS per RECIST 1.1 by blinded central radiologists' review of all participants with advanced gastric or GEJ adenocarcinoma who have progressed on 1 previous line of therapy, when treated with pembrolizumab compared to paclitaxel.

Hypothesis: Pembrolizumab prolongs PFS per RECIST 1.1 by blinded central radiologists' review of all participants (with advanced gastric or GEJ adenocarcinoma who have progressed on one previous line of therapy), compared to paclitaxel.

(2) **Objective**: To evaluate OS of all participants with advanced gastric or GEJ adenocarcinoma who have progressed on one previous line of therapy, when treated with pembrolizumab compared to paclitaxel.

Hypothesis: Pembrolizumab prolongs OS of all participants (with advanced gastric or GEJ adenocarcinoma) who have progressed on one previous line of therapy), compared to paclitaxel.

(3) **Objective:** To evaluate PFS per RECIST 1.1 by investigator assessment and PFS per irRECIST by blinded central radiologists' review, among participants with PD-L1 positive expression and all participants, when treated with pembrolizumab compared to paclitaxel.

(4) **Objective:** To evaluate the Time to Progression (TTP), Overall Response Rate (ORR), and Duration of Response (DOR), per RECIST 1.1 by blinded central radiologists' review and per RECIST 1.1 by investigator assessment among participants with PD-L1 positive expression and all participants, when treated with pembrolizumab compared to paclitaxel.

(5) **Objective**: Evaluate the safety and tolerability profile of pembrolizumab in participants with PD-L1 positive expression and all participants compared to paclitaxel.

3.3 Exploratory Objectives

(1) **Objective**: To evaluate score change of health-related quality-of-life (HRQoL) using the European Organisation for Research and Treatment of Cancer (EORTC) Quality-of-Life Questionnaire (QLQ)-Core Questionnaire (C30) and the EORTC QLQ-Gastic Cancer Module (STO22) from baseline among participants when treated with pembrolizumab compared to paclitaxel.

(2) **Objective**: To characterize utilities using European Quality-of-Life Scale 5 Dimension (EuroQol EQ-5D) among participants when treated with pembrolizumab compared to paclitaxel.

(3) **Objective**: To explore the relationship between genetic variation and response to the treatment(s) administered. Genomic variability may 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 Anti-PD-1 Blockage for Malignancy

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades [1]. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies [2] [3] [4] [5] [6]. 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), which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or programmed cell death ligand 2 [PD-L2]) [7] [8]. The structure of murine PD-1 has been resolved [9]. PD-1 and family members are type I

transmembrane glycoproteins containing an immunoglobulin Variable-type (IgV) 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 [7] [10] [11] [12]. 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 [13] [14]. 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 [15] [16]. Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells, as well as subsets of macrophages and dendritic cells [17]. 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 [18] [19] [20] [13]. Both ligands are type-I transmembrane receptors containing both IgV- and immunoglobulin constant (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 [13]. 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 [21].

In gastric cancer PD-L1 and PD-L2 overexpression have recently been associated with Epstein-Barr virus-positive tumors [22]. 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.

4.1.1.2 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 (US) for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab 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 monotherapy or in combination with other treatment modalities. Anti-mouse PD-1 or anti-mouse PD-L1 antibodies have demonstrated antitumor

responses as a monotherapy in models of squamous cell carcinoma, pancreatic carcinoma, melanoma and colorectal carcinoma. Blockade of the PD-1 pathway effectively promoted CD8+ T-cell infiltration into the tumor and the presence of interferon-γ, granzyme B, and perforin, indicating that the mechanism of action involved local infiltration and activation of effector T-cell function in vivo [23] [24] [25] [26] [27] [28]. Experiments have confirmed the in vivo efficacy of PD-1 blockade as a monotherapy as well as in combination with chemotherapy in syngeneic mouse tumor models (see the IB).

Clinical trials have demonstrated efficacy in participants 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, non-small cell lung cancer, 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 are available from a cohort of gastric adenocarcinoma participants studied in trial KEYNOTE 012 (KN012) [29]. Thirty-nine participants (19 from clinical trial sites in Asia and 20 from trial sites outside Asia) who had metastatic gastric or GEJ adenocarcinoma, Eastern Cooperative Oncology Group (ECOG) performance status (PS) 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 (Q2W). The number of prior systemic treatments for metastatic disease ranged from zero to greater than 4. The primary efficacy endpoint was ORR. Overall, the interim ORR is 30.8% (95% confidence interval [CI] 17.0%, 47.6%; all partial responses [PRs]), while the interim disease control rate (DCR) is 43.6% (95% CI 27.8%, 60.4%). ORR was similar in participants 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, participants had less prior therapy relative to the Asian participants, and that ORR in later line participants (≥3L) was higher in the Asian group (1 PR/7 participants in the non-Asia group, 4 PR/13 participants 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 participants 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 participants in KN012, single-agent pembrolizumab at 10 mg/kg Q2W was generally well tolerated, with the type, severity, and frequency of AEs similar to that observed in other indications (see the IB for information about AEs in other indications). There was 1 death reported in the gastric cancer cohort. This was a participant who had AEs of tracheomalacia (Grade 3) and hypoxia (Grade 5). The investigator considered the Grade 5 hypoxia related to the study treatment.

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 participants with metastatic disease. Refer to Section 4.1.3, Ongoing Clinical Trials, for results from the Phase Ib study of pembrolizumab in participants with gastric cancer (KN012). This study is designed to investigate if pembrolizumab monotherapy in second-line gastric cancer participants improves PFS and OS.

The gastric cancer proof-of-concept from KN012 data was obtained in participants with a PD-L1 positive expression only; no data are currently available regarding the performance of pembrolizumab in participants without a detectable PD-L1 expression. Due to the limited treatment opinions currently available, second-line participants without a detectable PD-L1 expression may benefit from pembrolizumab.

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 Q2W
- Clinical data showing meaningful improvement in benefit-risk including OS at 200 mg Q3W across multiple indications
- Pharmacology data showing full target saturation in both systemic circulation (inferred from pharmacokinetic [PK] data) and tumor (inferred from physiologically based PK analysis) at 200 mg Q3W

Among the 8 randomized dose-comparison studies, a total of 2262 participants 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 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 PK 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 participant covariates on exposure, has shown that the fixed dosing provides similar control of PK variability as weight-based dosing, with considerable overlap in the distribution of exposures from the 200 mg Q3W fixed dose and 2 mg/kg Q3W dose. Supported by these PK characteristics and given that 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 (IV) 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 [30].

Ramucirumab, an anti-vascular endothelial growth factor receptor 2 antibody, was approved by the US Food and Drug Administration (FDA) as monotherapy for second-line gastric cancer in April 2014, based on the results from the REGARD study [31]. The REGARD study was a Phase 3 study comparing ramucirumab monotherapy (8 mg/kg IV infusion on Days 1 and 15 every 4 weeks), versus best supportive care (BSC) in participants refractory to previous fluoropyrimidine treatment (with or without platinum). Ramucirumab significantly improved OS (5.2 month [mo] vs 3.8 mo with BSC, hazard ratio [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 [30]. RAINBOW was a Phase III study testing paclitaxel (80 mg/kg on Days 1, 8, and 15, of a 28-day cycle) with or without ramucirumab (8 mg/kg IV infusion on Days 1 and 15 of a 28-day cycle) in participants with metastatic gastric cancer refractory or progressive after first-line therapy with a platinum and a fluoropyrimidine. Median OS 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 PFS was 4.4 months and 2.9 months, respectively, with a HR of 0.635 (P < 0.0001). AEs of Grade ≥3 were somewhat greater with combination treatment vs paclitaxel alone and respectively, included incidences of 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 PFS and OS 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 CR assessment of immunotherapeutic agents such as pembrolizumab. Therefore, RECIST 1.1 will be used with the following adaptation, outlined in Section 7.1.2.6.4.1, termed irRECIST.

When feasible, participants 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 participants 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 Safety Endpoints

The primary safety objective of this trial is to characterize the safety and tolerability of pembrolizumab in participants with metastatic gastric cancer. The primary safety analysis will be based on participants who experienced toxicities as defined by CTCAE criteria. Safety will be assessed by quantifying the toxicities and grades experienced by participants who have received pembrolizumab compared to paclitaxel including SAEs and ECIs.

Safety will be assessed by reported AEs 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 will be analyzed including but not limited to all AEs, SAEs, fatal AEs, and laboratory changes. Furthermore, specific immune-related AEs (irAEs) will be collected and designated as immune-related ECIs as described in Section 7.2.3.2.

4.2.3.3 Exploratory Endpoints

4.2.3.3.1 Patient Reported Outcomes

As part of the exploratory analyses, participants will provide information regarding their HRQoL via the following assessment tools: EORTC QLQ-C30 and QLQ-STO22, electronic (eEQ-5D) questionnaires. Additionally, the Health Economic Assessment (HEA) form will also be collected. These measures are not pure efficacy or safety endpoints because they are affected by both disease progression and treatment tolerability.

eEORTC QLQ-C30 and eEORTC QLQ-STO22

The EORTC-QLQC30 is the most widely used cancer-specific HRQoL instrument, which contains 30 items and measures, 5 functioning dimensions (physical, role, cognitive, emotional, and social), 3 symptom items (fatigue, nausea/vomiting, pain), 6 single items (dyspnea, sleep disturbance, appetite loss, constipation, diarrhea, and financial impact), and a global health and quality-of-life scale [32]. This instrument has been translated and validated into 81 languages and used in more than 3000 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 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 (4 items), pain or discomfort (3 items), upper gastrointestinal (GI) symptoms (3 items), eating restrictions (5 items), emotional (3 items), dry mouth, hair loss, and body image.

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

eEQ-5D

The eEQ-5D is a standardized instrument for use as a measure of health outcome. The eEQ-5D will provide data for use in economic models and analyses including developing health utilities or quality adjusted life years. The 5 health state dimensions in this instrument include the following: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression [33]. Each dimension is rated on a three-point scale from 1 (extreme problem) to 3 (no problem). The eEQ-5D also includes a graded (0 to 100) vertical visual analog scale on which the participant rates his or her general state of health at the time of the assessment. The eEQ-5D will always be completed by participants 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.

Health Economic Assessment

The HEA form will be completed via an interview with the participant by trained study site personnel. The objective of the HEA form is for the site personnel to collect information from participants on all the non-study related health care contacts made throughout the study. The form captures non-study related healthcare visits, including healthcare provider visits, emergency room visits, and hospitalizations (including admission and discharge dates and

primary discharge diagnosis). The HEA is to be completed at various time points as specified in the Trial Flow Chart, beginning with Cycle 2 until 30 days post-treatment discontinuation.

4.2.3.3.2 Exploratory Biomarkers

Understanding genetic determinants of drug response is an important endeavor during medical research. This research will evaluate whether genetic variation within a clinical trial population correlates with response to the treatment(s) under evaluation. If genetic variation is found to predict efficacy or AEs, the data might inform future optimal use of therapies in the patient population. This research contributes to understanding genetic determinants of efficacy and safety associated with the treatments in this study.

Assays may include but are not be limited to:

Transcriptional Analyses

Messenger ribonucleic acid (RNA) expression profiling in archival material will be completed to assess expression of approximately 700 genes and attempt to define a gene set critical for clinical response to pembrolizumab (MK-3475). The hypothesis to be tested is that pembrolizumab (MK-3475) induces responses in tumors that reflect an inflamed/ immune phenotype based on gene expression signatures capturing PD-L1 and interferon-gamma transcriptional programs. Global profiling will also be pursued. Expression of individual genes related to the immune system may also be evaluated such as immune signatures and critical cytokines (e.g., interleukin-10). MicroRNA profiling may also be pursued in serum samples.

Proteomic Analysis

In addition to expression on the tumor tissue, PD-L1 can be shed from tumor and released into the blood. Enzyme-linked immunoassay can measure PD-L1 in serum and correlate this expression with response to pembrolizumab (MK-3475) therapy, as well as levels of PD-L1 immunohistochemistry or protein in the tumor. Blood would be a less invasive compartment compared to tumor from which to measure PD-L1 protein biomarker. In addition to this specific protein biomarker, both tissue and blood derivatives can be subjected to proteomic profiling studies using a variety of platforms that could include but are not limited to immunoassay, liquid chromatography/mass spectrometry. This approach could identify novel protein biomarkers that could aid in participant selection for pembrolizumab (MK-3475) therapy.

Gene Analyses

Additional biomarker research to identify factors important for pembrolizumab (MK-3475) therapy may also be pursued. For example, tumor and blood samples (including serum and plasma) from this study may undergo proteomic, genomic, metabolomic, and transcriptional analyses. Additional research may evaluate factors important for predicting responsiveness or resistance to pembrolizumab therapy and other immunologic targets.

Microsatellite Instability

Next generation sequencing of tumor deoxyribonucleic acid (DNA) has revealed certain tumors to be ‘hypermutated’. There is a potential that the hypermutated state may correlate with response to immunotherapy such as pembrolizumab (MK-3475) as ‘hypermutated’ cells

are assumed to be more immunogenic. Hypermutation in some cancers is driven by a defective DNA mismatch repair (MMR) process as a consequence of germline genetic defects in one of the MMR genes. MMR defects lead to microsatellite instability (MSI); the frequent deletion and insertion in arrays loci containing very short direct repeat sequences (microsatellites). Internal data from KN016 colorectal cancer trial has demonstrated exquisitely a selective response to pembrolizumab in those tumors that are MSI-high as detected by polymerase chain reaction and subsequent capillary electrophoresis. The hypothesis to be tested is that pembrolizumab induces responses in gastric tumors that have a high degree of MSI. DNA from tumors will be compared with that isolated from corresponding patient whole blood (representing normal DNA) or from adjacent normal tissue if blood sample is not available.

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

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

4.2.3.4 Future Biomedical Research

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

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

4.3 Benefit/Risk

Participants 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 participants participating in this clinical trial may be found in the accompanying IB and informed consent documents.

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

Male/Female 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 participant may also provide consent for Future Biomedical Research. However, the participant 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 the investigator. Tumor 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 PS of 0 or 1 on the ECOG Performance Scale.
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 participant needs to have the documentation of disease progression on first-line treatment. The disease progression can be confirmed by computed tomography (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 participant 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 participant 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, participants with discontinuation due to AEs 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, received permission for enrollment 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. Participants for whom newly-obtained endoscopic samples cannot be provided (e.g., inaccessible or participant safety concern) may submit an archived specimen.

    b. 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 participant 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.

    c. As of 20-MAR-2016, participants must be PD-L1 positive to be enrolled.

9. Participants with human epidermal growth factor receptor 2 (HER-2/neu) negative tumors are eligible. For participants with HER2/neu positive tumors or have an unknown tumor status, need to match the following:

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

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

10. Female participants 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 (Reference Section 5.7.2). Participants of childbearing potential are those who have not been surgically sterilized or have not been free from menses for >1 year.

Male participants 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.

11. Demonstrate adequate organ function as defined in Table 1. All screening labs should be performed within 10 days of 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 participant 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 participants with total bilirubin levels >1.5 ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 X ULN **OR** ≤ 5 X ULN for participants 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 participant is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants ≤1.5 X ULN unless participant is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants

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

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) 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 anticancer mAb within 4 weeks prior to study Day 1 or who has not recovered (i.e., ≤Grade 1 or at baseline) from AEs due to agents administered more than 4 weeks earlier.
6. Has had prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to study Day 1 or who has not recovered (i.e., ≤Grade 1 or at baseline) from AEs due to a previously administered agent.

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

   a. *If participant 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 requires active treatment. 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.
8. Has known active central nervous system metastases and/or carcinomatous meningitis. Participants with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least 4 weeks prior to the first dose of trial treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to trial treatment. This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability.
9. Has a history of (noninfectious) 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 participant's participation for the full duration of the trial, or is not in the best interest of the participant 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 immunotherapy including anti-PD-1, anti-PD-L1, or anti-PD-L2 agent, or if the participant has previously participated in Merck pembrolizumab (MK-3475) clinical trials.
15. Has a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).
16. Has known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C.
17. Has received a live vaccine within 30 days of planned start of study therapy.

    Note: Seasonal influenza vaccines for injection are generally inactivated flu vaccines and are allowed; however intranasal influenza vaccines (e.g., Flu-Mist®) 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	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 for Cycle 1 should begin within 3 days of randomization. However, every effort should be made to begin trial treatment on day of randomization.

All 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 will be responsible for recording the lot number, manufacturer and expiry date of any locally purchased product.

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

5.2.1 Dose Selection/Modification

5.2.1.1 Dose Selection (Preparation)

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

Preparation 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 for Pembrolizumab

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

AEs associated with pembrolizumab exposure may represent an immunologic etiology. These 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 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 1-2mg/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 1-2mg/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- 1mg/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 1-2mg/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 liothyroinine) 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).

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, participant vacation, and/or holidays). Participants 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 participant's study record.

In case toxicity does not resolve to Grade 0-1 within 12 weeks after the last infusion, trial treatment should be discontinued after consultation with the Sponsor. With investigator and Sponsor agreement, participants with a laboratory AE still at Grade 2 after 12 weeks may continue in the trial only if asymptomatic and controlled.

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 4), 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 4 Criteria for Paclitaxel Treatment on Each Cycle

Parameter	Criterion
Absolute neutrophil count	≥1.0 × 10^9/L
Platelet count	≥75 × 10^9/L
Bilirubin	≤1.5 × ULN
AST/ALT	≤3 × ULN, or <5 × 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 5), the investigator should institute treatment measures according to the best available medical practice.

Table 5 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 IV and dexamethasone 8-20 mg IV (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 IV diphenhydramine and dexamethasone (per institutional guidelines). Add epinephrine or bronchodilators if indicated. The participant should be removed from paclitaxel treatment.	At first occurrence

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

- An unacceptable AE/toxicity (e.g., a persistent moderate toxicity that is intolerable to the participant) 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 2 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, participant vacation, and/or holidays). Participants 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 participant's study record.

5.2.2 Timing of Dose Administration

All trial treatments may be administered on an outpatient basis.

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 participant 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 recalculated to account for the weekly dosing visits.

5.2.2.1 Pembrolizumab

Pembrolizumab should be administered on Day 1 of each three-week cycle 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 4-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 participant's baseline BSA. Subsequent doses of paclitaxel must be recalculated if there is a ≥10% change (increase or decrease) in BSA from baseline; subsequent doses may be recalculated if there is a <10% change (increase or decrease) in BSA 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 orally (PO) 12 and 6 hours or (IV) 30-60 minutes before paclitaxel), an antihistamine (H1 antagonist) such as diphenhydramine hydrochloride 50 mg IV (or equivalent), cimetidine (H2 antagonist) 300 mg IV or equivalent, and an antiemetic (such as ondansetron 8 mg dose PO or 0.15 mg/kg IV 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 (CRF).

5.2.3 Trial Blinding/Masking

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.

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

5.3 Randomization or Treatment Allocation

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

5.4 Stratification

Randomization will be stratified according to the following factors:

1. Geographic region (Europe/Israel/North America/Australia vs. Asia (including Japan, Korea, Hong Kong, Taiwan, Malaysia, Philippines, Singapore) vs. Rest of World (including South America)

2. TTP on first-line therapy (<6 months vs. ≥6 months)
3. PD-L1 expression status (positive vs. negative)

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.

Acceptable Concomitant Medications

All treatments that the investigator considers necessary for a participant's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the CRF including all prescription, over-the-counter (OTC), 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 28 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 and ECIs as defined in Section 7.2.

5.5.1 Prohibited Concomitant Medication

Participants are prohibited from receiving the following therapies during the Screening and Treatment Phase (including retreatment for post-CR 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, bacille Calmette-Guerin, 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., Flu - Mist®) are not allowed.

- Pembrolizumab arm only: Systemic glucocorticoids for any purpose other than to modulate symptoms from an ECI of suspected 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).

Participants 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. Participants 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, premedication with steroids is acceptable.

5.6 Rescue Medications & Supportive Care

5.6.1 Supportive Care Guidelines

Participants 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 below. 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 the event is determined not to be related, 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.

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

- **Diarrhea/Colitis**:

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

  - All participants who experience 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. For Grade 2 or higher diarrhea, consider GI consultation and endoscopy to confirm or rule out colitis.
  - For **Grade 2 diarrhea/colitis** that persists greater than 3 days, administer oral corticosteroids.
  - For **Grade 3 or 4 diarrhea/colitis** that persists >1 week, treat with IV steroids followed by high dose oral steroids.
  - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

- **Type 1 diabetes mellitus** (TIDM, if new onset, including diabetic ketoacidosis [DKA]) or ≥Grade 3 hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA):
  - For **T1DM** or **Grade 3-4** Hyperglycemia
    - Insulin replacement therapy is recommended for TIDM and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria.
    - Evaluate patients with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.

- **Hypophysitis**:
  - For **Grade 2** events, treat with corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
  - For **Grade 3-4** events, treat with an initial dose of IV corticosteroids followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

- **Hyperthyroidism or Hypothyroidism**:

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

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

- **Hepatic**:
  - For **Grade 2** events, monitor liver function tests more frequently until returned to baseline values (consider weekly).
    - Treat with IV or oral corticosteroids
  - For **Grade 3-4** events, treat with IV corticosteroids for 24 to 48 hours.
  - When symptoms improve to Grade 1 or less, a steroid taper should be started and continued over no less than 4 weeks.
- **Renal Failure or Nephritis**:
  - For **Grade 2** events, treat with corticosteroids.
  - For **Grade 3-4** events, treat with systemic corticosteroids.
  - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
- **Management of Infusion Reactions**: Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion.

Table 6 below shows treatment guidelines for participants who experience an infusion reaction associated with administration of pembrolizumab (MK-3475).

Table 6 Infusion Reaction Treatment Guidelines

NCI-CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the participant 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 and monitor symptoms.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose. **Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.**	Participant may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab (MK-3475) with: Diphenhydramine 50 mg PO (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg PO (or equivalent dose of antipyretic).
Grades 3 or 4 Grade 3: Prolonged (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: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **Participant is permanently discontinued from further trial treatment administration.**	No subsequent dosing
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.		

5.6.2 Supportive Care Guidelines for Paclitaxel

Palliative and supportive care for other disease-related symptoms and for toxicity associated with treatment will be offered to participants within the paclitaxel arm of this trial. Supportive care measures may include, but are not limited to, antidiarrheal agents, antiemetic agents, opiate and non-opiate 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 electronic case report form (eCRF). Appropriate management of hypersensitivity reactions is described in Section 5.2.1.2.2 and Table 5. The use of other specific supportive care agents is 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 IV hydration) and associated with fever or severe (Grade 3 or 4) neutropenia, broad-spectrum antibiotics may be prescribed. Participants with severe diarrhea or any diarrhea associated with severe nausea or vomiting must be hospitalized for IV 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 participant. 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 (absolute neutrophil count [ANC] $<1.0 \times 10^9$/L with temperature ≥38.5°C).

Erythroid Growth Factors: The use of erythroid-stimulating factors (e.g., erythropoietin) is permitted at the discretion of the investigator based on American Society of Clinical Oncology and FDA guidelines, or according to local guidelines [34] [35].

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

Participants 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 ≥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 2 birth control methods can either be 2 barrier methods or a barrier method plus a hormonal method to prevent pregnancy. Participants 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. Participants 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 participant.

Participants 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 participant will not reliably comply with the requirements for contraception, that participant should not be entered into the study.

5.7.3 Use in Pregnancy

If a participant inadvertently becomes pregnant while on treatment with pembrolizumab or paclitaxel, the participant will immediately be removed from the study. The site will contact the participant at least monthly and document the participant'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 an SAE (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

participant 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, participants 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.

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 per the terms outlined in Section 7.1.2.6.4.
- Unacceptable adverse experiences as described in Section 5.2.1.2.
- Intercurrent illness that prevents further administration of treatment.
- Investigator's decision to withdraw the participant.
- The participant has a confirmed positive serum pregnancy test.
- The participant has a positive urine drug screen at any time during the course of the trial.
- Noncompliance with trial treatment or procedure requirements.
- The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or Sponsor, placed the participant at unnecessary risk from continued administration of study drug.

- Completed 35 administrations (approximately 2 years) of uninterrupted treatment with pembrolizumab.
- Administrative reasons.

  Note: Participants who stop pembrolizumab after 35 administrations (approximately 2 years) may be eligible for up to one year of additional study treatment if they progress after stopping study treatment, provided they meet the requirements detailed in Section 7.1.5.5.

The End of Treatment and Follow-up visit procedures are listed in Section 6 (Trial Flow Chart) and Section 7.1.5 (Visit Requirements). After the end of treatment, each participant will be followed for 30 days for AE monitoring (SAEs will be collected for 90 days after the end of treatment or 30 days after the end of treatment if the participant initiates new anticancer therapy, whichever is earlier, as described in Section 7.2.3.1). Participants who discontinue for reasons other than PD will have post-treatment follow-up for disease status until disease progression, initiating a non-study cancer treatment, withdrawing consent or becoming lost to follow-up. After documented disease progression each participant will be followed by telephone for OS until death, withdrawal of consent, or the end of the study, whichever occurs first.

5.8.2 Discontinuation of Study Therapy after Complete Response

Discontinuation of treatment may be considered for participants who have attained a confirmed CR that have been treated for at least 24 weeks with pembrolizumab and had at least 2 treatments with pembrolizumab beyond the date when the initial CR was declared. Participants 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 participant meets the safety parameters listed in the Inclusion/Exclusion criteria, and the trial is open. Participants 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, all visits and procedures, as outlined in the trial flowchart, should be completed.

5.8.3 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. The overall trial ends when the last subject completes the last trial visit, discontinues from the trial or is lost to follow-up (ie, the subject is unable to be contacted by the investigator). Upon study completion, subjects will be 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 participants
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 participant 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	
ePROs (HRQoL Measures)[i]		X	X	X	X	X[i]		X	X		
Health Economic Assessment (HEA)[i]			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	X	X	X	X	X	X	X			
Post-study Anticancer Therapy Status										X	X
Survival Status[c]		←								→	X
Trial Treatment Administration											
Pembrolizumab[k]		X	X	X	X	X	X				
Laboratory Procedures/Assessments: Analysis performed by LOCAL laboratory											
Pregnancy Test – Urine or Serum β-HCG[l]	X										
PT/INR and aPTT[m]	X										
CBC with Differential[n]	X		X	X	X	X	X[n]	X	X[n]		
Chemistry Panel[n]	X		X	X	X	X	X[n]	X	X[n]		

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		Discon	Safety Follow-up	Follow-Up Visits[b]	Survival Follow-up[c]
						5	6				
								At time of discon	30 days post discon	Every 6 weeks post discon	Every 12 weeks
Urinalysis[n]	X										
T3, FT4 and TSH	X [n]		X		X		X		X		
Serum carcinoembryonic antigen (CEA) [n]	X			X		X[n]					
Serum CA 19-9[n]	X			X		X[n]					
Laboratory Procedures/Assessments: Analysis performed by CENTRAL laboratory											
Blood for Genetics[o]		X									
Correlative Blood Samples (DNA)[p]		X	X	X				X			
Correlative Blood Samples (RNA)[p]		X	X	X				X			
Correlative Blood Samples (plasma)[p]		X									
Correlative Blood Samples (serum)[p]		X									
Efficacy Measurements											
Tumor Imaging[q]	X			X		X		X[r]		X	
Tumor Tissue Collection											
Archival and/or Newly-Obtained Tissue Collection	X[s]										

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 participants 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 anticancer treatment, (2) disease progression as assessed by the central imaging vendor, (3) death, or (4) the end of the study, whichever occurs first.
c. After the start of new anticancer treatment or documented disease progression by the central imaging vendor, the participant 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 participant 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). Informed consent may be signed prior to the Screening Period specified above in the Trial Flow Chart (-28 to -1 days) 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.

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		Discon	Safety Follow-up	Follow-Up Visits[b]	Survival Follow-up[c]
						5	6				
								At time of discon	30 days post discon	Every 6 weeks post discon	Every 12 weeks

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 occurring within 30 days after the last dose of trial treatment. Report all SAEs (related and unrelated to trial treatment) and ECIs occurring up until 90 days after the last dose of trial treatment or 30 days following last dose of trial treatment if the participant 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 electronic Patient Reported Outcomes (ePROs) 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 and HEA; an exception to this recommendation may occur at the treatment Discontinuation Visit where participants may have already been notified of their disease status or an AE evaluation is known prior to them arriving to the clinic. All ePROs (except the HEA) are to be performed at Cycle 1, Cycle 2, Cycle 3, Cycle 4, Cycle 5, Cycle 7, and Cycle 9. After Week 24, ePROs 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. The HEA is to be completed by trained study site personnel and will begin at Cycle 2 then follow the above listed time points. If the participant does not complete the ePROs, 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. Pembrolizumab should be administered on Day 1 of each three-week cycle after all procedures/assessments have been completed.

l. For women of reproductive potential, a serum pregnancy test should be performed within 72 hours prior to first dose of trial treatment. A urine test can be considered if serum is not appropriate. Pregnancy tests (serum and/or urine tests) should be repeated if required by local guidelines.

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

n. 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. Complete Blood Count (CBC) with Differential and Chemistry panel is 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. 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.

o. 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 participant 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.

p. Whole blood sample for correlative studies should be collected at Cycle 1, Day 1- Predose, Cycle 2 Day 1- Predose, Cycle 3 Day 1 Predose and again at treatment discontinuation. Blood for serum and blood for plasma to be collected only prior to Cycle 1 Day 1. See Procedures Manual.

q. 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 central imaging vendor.

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		Discon	Safety Follow-up	Follow-Up Visits[b]	Survival Follow-up[c]
						5	6				
								At time of discon	30 days post discon	Every 6 weeks post discon	Every 12 weeks

r. In participants 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.
s. Endoscopic biopsies are permitted. Any leftover tumor will be stored for future biomedical research if the participant signs the FBR consent.

6.2 Trial Flow Chart – Initial Treatment Phase for Paclitaxel Arm

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
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	
ePROs (HRQoL Measures) [i]		X			X		X	X	X		
Health Economic Assessment (HEA)[i]					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	X	X	X	X	X	X	X			
Post-study Anticancer Therapy Status										X	X
Survival Status [c]		←	-	-	-	-	-	-	-	→	X
Trial Treatment Administration											
Paclitaxel[k]		X	X	X	X	X	X				
Laboratory Procedures/Assessments: Analysis performed by LOCAL laboratory											
Pregnancy Test – Urine or Serum β-HCG[l]	X										
PT/INR and aPTT [m]	X										
CBC with Differential[n]	X		X	X	X	X	X	X	X		
Chemistry Panel[n]	X		X	X	X	X	X	X	X		
Urinalysis [n]	X										
T3, FT4 and TSH	X [n]		X				X		X		

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
Serum carcinoembryonic antigen[n]	X						X[n]				
Serum CA19-9[n]	X						X[n]				
Laboratory Procedures/Assessments: Analysis performed by CENTRAL laboratory											
Blood for Genetics[o]		X									
Correlative Blood Samples (DNA)[p]		X			X			X			
Correlative Blood Samples (RNA)[p]		X			X			X			
Correlative Blood Samples (plasma)[p]		X									
Correlative Blood Samples (serum)[p]		X									
Efficacy Measurements											
Tumor Imaging[q]	X						X[q]	X[r]		X	
Tumor Tissue Collection											
Archival and/or Newly-Obtained Tissue Collection	X[s]										

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 participants 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 anticancer treatment, (2) disease progression as assessed by the central imaging vendor, (3) death, or (4) the end of the study, whichever occurs first.

c. After the start of new anticancer treatment or documented disease progression by the central imaging vendor, the participant should be contacted by telephone 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 participant 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). Informed consent may be signed prior to the Screening Period specified above in the Trial Flow Chart (-28 to -1 days) 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.

h. Record all AEs occurring within 30 days after the last dose of trial treatment. Report all SAEs (related and unrelated to trial treatment) and ECIs occurring up until 90 days after

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

the last dose of trial treatment or 30 days following last dose of trial treatment if the participant 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 electronic Patient Reported Outcomes (ePROs) 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 and HEA; an exception to this recommendation may occur at the treatment Discontinuation Visit where participants may have already been notified of their disease status or an AE evaluation is known prior to them arriving to the clinic. All ePROs (except the HEA) 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. The HEA is to be completed by trained study site personnel and will begin at Cycle 2 then follow the above listed time points. If the participant does not complete the ePROs, 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. Paclitaxel should be administered on Day 1, 8, and 15 of each 28-day (4-week) cycle after all procedures/assessments have been completed.

l. For women of reproductive potential, a serum pregnancy test should be performed within 72 hours prior to first dose of trial treatment. A urine test can be considered if serum is not appropriate. Pregnancy tests (serum and/or urine tests) should be repeated if required by local guidelines.

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

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

o. 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 participant 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.

p. Whole blood sample for correlative studies should be collected at Cycle 1, Day 1- Predose, Cycle 2 Day 1- Predose, Cycle 3 Day 1 Predose and again at treatment discontinuation. Blood for serum and blood for plasma to be collected only prior to Cycle 1 Day 1. See Procedures Manual.

q. 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 central imaging vendor.

r. In participants 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.

s. Endoscopic biopsies are permitted. Any leftover tumor will be stored for future biomedical research if the participant 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	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]:		± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 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	X	X	X	X	X	X			
Pembrolizumab Administration[i]	X	X	X	X	X	X				
Post-study Anticancer Therapy Status									X	X
Survival Status[c]	←	----	----	----	----	----	----	----	→	X
Laboratory Procedures/Assessments: Analysis performed by LOCAL laboratory										
Pregnancy Test – Urine or Serum β-HCG[j]	X									
PT/INR and aPTT[k]	X									
CBC with Differential[l]	X	X	X	X	X	X[k]	X	X		
Chemistry Panel[l]	X	X	X	X	X	X[k]	X	X		
Urinalysis[l]	X									
T3, FT4 and TSH[l]	X		X		X			X		
Efficacy Measurements										
Tumor Imaging[m]	X		X			X	X[n]		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 participants 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 anticancer treatment, (2) disease progression as assessed by the central imaging vendor, (3) death, or (4) the end of the study, whichever occurs first.
c. After the start of new anticancer treatment or documented disease progression by the central imaging vendor, the participant should be contacted by telephone 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

Trial Period:	Treatment Cycles[a]						End of Treatment	Post-Treatment		
Treatment Cycle:	1	2	3	4	5	Cycle 6 and beyond	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]:		± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 7	± 7

participants that have a death event previously recorded).

d. In general, the window for each visit is ± 3 days unless otherwise noted.
e. Participants 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 occurring within 30 days after the last dose of trial treatment. Report all SAEs (related and unrelated to trial treatment) and ECIs occurring up until 90 days after the last dose of trial treatment or 30 days following last dose of trial treatment if the participant initiates new anticancer 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. Participants who restart treatment should resume at the same dose and schedule which they were receiving prior to discontinuation.
j. For women of reproductive potential, a serum pregnancy test should be performed within 72 hours prior to first dose of trial retreatment. A urine test can be considered if serum is not appropriate. Pregnancy tests (serum and/or urine tests) should be repeated if required by local guidelines.
k. Coagulation factors (PT/INR and aPTT) should be tested as part of the screening procedures for all participants.
l. 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.
m. 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.
n. In participants 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.

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.

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 clinically significant by the investigator. Details regarding the participant's gastric or GEJ adenocarcinoma will be recorded separately and not listed as medical history.

Please note that if the participant has lost at least 15 lbs. (6.8 kg.) over the 3 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 participant'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 participant within 30 days before starting the trial. Details regarding the participant'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 participant during the trial from the time of signing the ICF 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 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 Randomization Number

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

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

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 doses 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 Monitoring

The investigator or qualified designee will assess each participant to evaluate for potential new or worsening AEs as specified in the Trial Flow Chart and more frequently if clinically indicated. AEs will be graded and recorded throughout the study and during the follow-up period according to NCI-CTCAE Version 4.0 (see Appendix 12.5). Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

For participants receiving treatment with pembrolizumab all AEs of unknown etiology associated with pembrolizumab exposure should be evaluated to determine if it is possibly an ECI of a potentially immunologic etiology (termed irAEs); see Section 7.2.3.2.

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 electrocardiography (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 Performance Status

The investigator or qualified designee will assess ECOG PS (see Appendix 12.6) 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 participant 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). Imaging may be more frequent if clinically indicated. Imaging should not be delayed for delays in cycle starts or extension of cycle intervals.

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

Per RECIST 1.1, response should be confirmed by a repeat radiographic assessment not less than 4 weeks from the date the response was first documented. The scan for confirmation of response may be performed at the earliest 4 weeks after the first indication of response, or at the next scheduled scan (i.e., 6 weeks later), whichever is clinically indicated.

At the time of the initial PD by RECIST 1.1 imaging scans should be sent to central vendor to verify progressive disease. If PD is verified, the investigator may choose to continue treatment if the participant is clinically stable and repeat imaging in 4 weeks to confirm PD (by the site) and then follow irRECIST. Imaging should continue to be performed until documented disease progression, the start of new anticancer treatment, withdrawal of consent, death, or the end of the trial, whichever occurs first. For participants receiving pembrolizumab, per irRECIST, disease progression should be confirmed at least 4 weeks after the first scan indicating PD in clinically stable participants. Participants who have unconfirmed disease progression may continue on treatment until progression is confirmed, provided they have met the conditions detailed in Section 7.1.2.6.4.1.

In clinically stable participants, disease progression may be confirmed by the site at least 4 weeks after the first scan indicating PD.

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 Assessment of Disease

Standard RECIST 1.1 will be applied by the central imaging vendor 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 study therapy). Scans showing site-assessed PD should be submitted to the central imaging vendor immediately. The site will be notified when the imaging vendor verifies disease progression using RECIST 1.1.

7.1.2.6.4.1 irRECIST

Following PD by RECIST, sites will assess tumor response and progression per irRECIST for participants receiving pembrolizumab as this data will be collected in the clinical database.

irRECIST is RECIST 1.1 adapted for use with immunotherapies as described in the Procedure Manual and irRECIST Tip Sheet.

If initial imaging shows PD, tumor assessment may be repeated by the site at least 4 weeks later in order to confirm PD with the option of continuing treatment until this scan is obtained for clinically stable participants (see Table 7). Clinically stable is defined by the following criteria:

- Absence of signs and symptoms indicating disease progression
- No decline in ECOG PS
- Absence of rapid progression of disease
- Absence of progressive tumor at critical anatomical sites (e.g., cord compression) requiring urgent alternative medical intervention

Table 7 Imaging and Treatment after 1st Radiologic Evidence of Progressive Disease

	Clinically Stable		Clinically Unstable	
	Imaging	**Treatment**	**Imaging**	**Treatment**
1st radiologic evidence of PD	Repeat imaging at ≥4 weeks to confirm PD	May continue study treatment at the investigator's discretion while awaiting confirmatory scan.	Repeat imaging at ≥4 weeks to confirm PD if possible	Discontinue treatment
Repeat scan confirms PD	No additional imaging required	Discontinue treatment (exception is possible upon consultation with Sponsor).	No additional imaging required	N/A
Repeat scan shows SD, PR or CR	Continue regularly scheduled imaging assessments every 6 weeks	Continue study treatment at the investigator's discretion.	Continue regularly scheduled imaging assessments every 6 weeks	May restart study treatment if condition has improved and/or clinically stable per investigator's discretion

In determining whether or not the tumor burden has increased or decreased, investigators should consider all target lesions as well as non-target lesions (please refer to the irRECIST Tip Sheet). Participants that are deemed clinically unstable are not required to have repeat imaging for confirmation. If radiologic progression is confirmed, it is recommended that the participant be discontinued from trial treatment unless, in the investigator's opinion, the participant is deriving benefit from treatment. Clinically stable participants as defined above may continue to receive trial therapy after discussion with the Sponsor.

If a participant has unconfirmed progression of disease and is clinically stable, it is at the discretion of the investigator to continue treating the participant with the assigned treatment per protocol until progression of disease is confirmed at least 28 days from the date of the scan suggesting progression of disease. If progression is not confirmed on the subsequent scan, the participant should continue to receive study therapy and radiographic scans obtained to monitor for disease status every 6 weeks (42 ± 7 days). The same imaging technique, acquisition, and processing parameters should be used in a participant throughout the trial. Details are provided in the Site Imaging Manual.

NOTE: In participants who discontinue study therapy without documented disease progression, every effort should be made to continue monitoring their disease status by radiologic imaging every 6 weeks (± 7 days) until (1) the start of new anticancer treatment, (2) disease progression (3) death, or (4) the end of the study, whichever occurs first. If radiologic progression is not confirmed, then the participant should resume or continue trial treatment and have their next scan according to the protocol schedule. During the follow-up period, imaging will be repeated every 12 weeks (± 7 days). See the Trial Flow Charts in Section 6 for information about the Follow-up Visits.

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 FFPE block specimens are preferred to slides. The specimen will be evaluated at a central laboratory facility for expression status of PD-L1.

Note: A fine needle aspirate 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.

If the participant 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.

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 participant has provided the relevant informed consent.

Details regarding time points for blood collection are outlined in the Trial Flow Chart – Section 6. Further details can also be found in Section 4.2.3.3 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 electronically by participants. It is strongly recommended that the electronic EORTC QLQ-C30, EORTC QLQ-STO22 and EuroQol EQ-5D is completed by the participant prior to drug administration, AE evaluation and disease status notification; an exception to this recommendation may occur at the treatment Discontinuation Visit. ePROs will be administrated in the following order: EuroQol EQ-5D first, then EORTC QLQ-C30, and lastly the EORTC QLQ-STO22 at the time points specified in the Trial Flow Chart. The HEA form will be completed via an

interview with the participant by trained study site personnel after the participant completes all other questionnaires. The form captures non-study related healthcare visits, including healthcare provider visits, ER visits, and hospitalizations (including admission and discharge dates and primary discharge diagnosis).

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 participant 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]		

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, predose laboratory procedures can be conducted up to 72 hours prior to dosing for the pembrolizumab arm. For participants 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 be acceptable prior to each dose of trial treatment.

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 medication, 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. The results of the pregnancy testing will not be recorded.

7.1.3.3 Pharmacokinetic/Pharmacodynamic Evaluations

The accumulation of robust PK and anti-drug antibodies (ADA) data has allowed for the adequate characterization of the clinical pharmacology of pembrolizumab across indications. Therefore, upon approval of Amendment 11, each site should stop the collection of PK and ADA samples for all participants. Blood samples for PK and ADA collected prior to Amendment 11 will be stored and analysis will be performed if required.

7.1.3.4 Planned Genetic Analysis Sample Collection

Sample collection, storage and shipment instructions for planned genetic analysis samples will be provided in the Procedures Manual.

7.1.3.5 Future Biomedical Research

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

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

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

7.1.4.2 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 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

Approximately 28 days prior to randomization, potential participants 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 – Trial Flow Chart.

Results of a test performed prior to the participant 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 and ECOG PS are to be performed within 10 days prior to the first dose of trial treatment.
- For women of reproductive potential, a serum pregnancy test will be performed within 72 hours prior to the first dose of trial treatment. A urine test may be considered if serum test is not appropriate.
- Baseline tumor imaging will be performed within 14 days prior to randomization for all participants. 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.

Participants 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. Participants who are rescreened will retain their original screening number.

7.1.5.2 Treatment Period

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

7.1.5.3 Discontinuation Visit

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 – Trial Flow Chart. Specific procedure-related details are provided above in Section 7.1 – Trial Procedures. Additional details regarding participant 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 anticancer treatment, whichever comes first. All AEs that occur prior to the Safety Follow-up Visit should be recorded.

Participants 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 anticancer therapy, whichever occurs first. SAEs and ECIs will be collected for 90 days after the end of treatment or 30 days following last dose of trial treatment if the participant initiates new anticancer therapy, whichever occurs 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, one after the Treatment Period and one after the Second Course Phase.

7.1.5.4.2 Follow-up Visits

Participants 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 anticancer therapy, disease progression determined by the central imaging vendor, death, or at end of study. Information regarding post-study anticancer treatment will be collected if new treatment is initiated.

Participants 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 participant experiences confirmed disease progression confirmed by central review or starts a new anticancer therapy, the participant 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 IA, and/or FA. 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 previously recorded death event in the collection tool).

7.1.5.5 Second Course Phase (Retreatment Period)

Participants on the pembrolizumab arm who stop treatment with stable disease (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 participant 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 2 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 (approx. 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 anticancer treatment since the last dose of pembrolizumab.
    - Has a performance status of 0 or 1 on the ECOG PS.
    - Demonstrates adequate organ function as detailed in Section 5.1.2.
    - Female participant of childbearing potential should have a negative serum or urine pregnancy test within 72 hours prior to receiving retreatment with study medication.
    - Female participant 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). Participants of child bearing potential are those who have not been surgically sterilized or have been free from menses for >1 year.
    - Male participant 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 participant's participation for the full duration of the trial or is not in the best interest of the participant to participate, in the opinion of the treating investigator.

Participants who restart treatment will be re-treated 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.

Participants 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 randomization/treatment allocation must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

From the time of randomization/treatment allocation through 30 days following cessation of treatment, all adverse events must be reported by the investigator. Such events will be recorded at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in Section 7.2.3.1. The investigator will make every attempt to follow all subjects with non-serious adverse events for outcome.

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

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

For purposes of this trial, an overdose will be defined as any dose exceeding the prescribed dose for 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 within 24 hours to the Sponsor either by electronic media or paper. Sponsor Contact information can be found in the Investigator Trial File Binder (or equivalent).

7.2.2 Reporting of Pregnancy and Lactation to the Sponsor

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

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

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

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

For the time period beginning at randomization/treatment allocation through 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, any ECI, or follow up to an ECI, whether or not related to the Sponsor's product, must be reported within 24 hours to the Sponsor, either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

Events of clinical interest for this trial include:

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

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

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

3. Additional Adverse Events:

Participants should be assessed for possible ECIs prior to each dose. Lab results should be evaluated, and participants should be asked for signs and symptoms suggestive of an immune-related event. Participants who develop an ECI thought to be immune-related should have additional testing to rule out other etiologic causes. If lab results or symptoms indicate a possible immune-related ECI, then additional testing should be performed to rule out other etiologic causes. If no other cause is found, then it is assumed to be immune-related.

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 participants 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 external Data Monitoring Committee (eDMC) regarding the trial.

7.3.3 Data Monitoring Committee

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

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

Specific details regarding composition, responsibilities, and governance, including the roles and responsibilities of the various members and the Sponsor protocol team; meeting facilitation; the trial governance structure; and requirements for and proper documentation of DMC reports, minutes, and recommendations will be described in a separate charter that is reviewed and approved by the DMC. The DMC will monitor the trial at an appropriate frequency, as described in the detailed DMC charter. The DMC will also make recommendations to the Sponsor protocol team regarding steps to ensure both subject safety and the continued ethical integrity of the trial.

An eDMC recommendation will be communicated to the Sponsor as agreed to in the Document Review Committee charter.

Treatment-level results of the IA 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 participant safety and continued ethical integrity of the trial.

Limited additional Sponsor personnel may be unblinded to the treatment-level results of the IA, if required, in order to act on the recommendations of the eDMC or facilitate regulatory filing after the IA. The extent to which individuals are unblinded with respect to results of IA will be documented by the unblinded statistician. Additional logistical details and data monitoring guidance 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 unblinding, will be documented in a supplemental SAP (sSAP) and referenced in the Clinical Study Report (CSR) for the study. Post hoc exploratory analyses will be clearly identified in the CSR.

In this section, "PD-L1 positive participants" means "participants with tumor PD-L1 expression", and "PD-L1 negative participants" means "participants with no detectable PD-L1 expression".

8.1 Statistical Analysis Plan Summary

Key elements of the statistical analysis plan are summarized in Table 10 below; the comprehensive plan is provided in Sections 8.2 through 8.12.

Table 10 Statistical Analysis Plan

Study Design Overview	A Phase III, Randomized, Open-label Clinical Trial of Pembrolizumab (MK-3475) versus Paclitaxel in Subjects with Advanced Gastric or Gastroesophageal Junction Adenocarcinoma who Progressed after First-Line Therapy with Platinum and Fluoropyrimidine
Treatment Assignment	Approximately up to 720 participants will be randomized in a 1:1 ratio to receive pembrolizumab or paclitaxel. Stratification factors are geographic region (Europe/Israel/North America/Australia vs. Asia vs. Rest of World), TTP on first-line therapy (<6 months vs. ≥6 months) and PD-L1 status (positive vs. negative). This is an open-label study.
Analysis Populations	Efficacy: Intention-to-Treat (ITT) Safety: All Subjects as Treated (ASaT)
Primary Endpoints	1. PFS per RECIST 1.1 by blinded central radiologists' review in PD-L1 positive participants 2. OS in PD-L1 positive participants
Key Secondary Endpoints	1. PFS per RECIST 1.1 by blinded central radiologists' review in all participants 2. OS in all participants
Statistical Methods for Key Efficacy Analyses	The primary and key secondary 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 HR will be done using a stratified Cox regression model. Event rates over time will be estimated within each treatment group using the Kaplan-Meier method.

Statistical Methods for Key Safety Analyses	The analysis of safety results will follow a tiered approach. The tiers differ with respect to the analyses that will be performed. Safety parameters or adverse experiences of special interest that are identified *a priori* constitute "Tier 1" safety endpoints that will be subject to inferential testing for statistical significance with p-values and 95% CIs provided for between-group comparisons. Other safety parameters will be considered Tier 2 or Tier 3. Tier 2 parameters will be assessed via point estimates with 95% CIs provided for between-group comparisons; only point estimates by treatment group are provided for Tier 3 safety parameters. There are no Tier 1 events in this trial. The between-treatment difference will be analyzed using the Miettinen and Nurminen method [36].
Interim Analysis	One interim analysis (IA) will be performed in this study. Results will be reviewed by an eDMC. The IA is summarized below. Details are provided in Section 8.7. • IA o Timing: To be performed after: (1) enrollment is completed (2) approximately 240 OS events have been observed among PD-L1 positive participants and 3) a minimum of 260 PFS events have been observed among PD-L1 positive participants o Purpose: IA for OS and main efficacy analysis for PFS • FA o Timing: at least 290 OS events have been observed among PD-L1 positive participants, or approximately 15 months after last patient randomized, whichever is later. o Purpose: Main efficacy analysis for 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 0.35% allocated to PFS and 2.15% allocated to OS hypotheses. Within each endpoint, the Type-I error rate for hypotheses on different populations will then be controlled by step-down testing procedure (PD-L1 positive participants first and then all participants). If PFS hypotheses are rejected for both populations (PD-L1 positive and all participants), the corresponding alpha level can be shifted to the hypotheses for the OS endpoint using the graphical approach of Maurer and Bretz [37].
Sample Size and Power	The planned sample size is approximately up to 720 participants. The FA of this study will complete after at least 290 OS events have been observed in the PD-L1 positive participants, or approximately 15 months after last patient randomized, whichever is later. For the primary endpoint PFS in the PD-L1 positive participants, the trial has 99% (97%) power to demonstrate that pembrolizumab is superior to paclitaxel at a one-sided 0.35% alpha-level, if the underlying HR of PFS is 0.5 (0.6). For primary endpoint OS in the PD-L1 positive participants, the trial has 91% power to demonstrate that pembrolizumab is superior to paclitaxel at a one-sided 2.15% alpha-level, if the underlying HR of OS is 0.67 and 290 OS events are observed.

8.2 Responsibility for Analyses/In-House Blinding

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

Although the trial is open-label, analyses or summaries generated by randomized treatment assignment, actual treatment received, and/or PD-L1 biomarker status will be limited and documented. In addition, the independent radiologist(s) will perform the central imaging review without knowledge of treatment group assignment.

The IVRS Vendor will generate the randomized allocation schedule(s) for study treatment assignment. The algorithm for the randomized allocation of participants will be implemented in an IVRS.

Planned interim analyses are described in Section 8.7. IA will be performed when enrollment is completed. Access to the allocation schedule for this study will be restricted to an external unblinded statistician and, as needed, a scientific programmer performing the analysis, who will have no other responsibilities associated with the study.

Treatment-level results of the interim analyses will be provided by the unblinded statistician to the eDMC. Limited additional Sponsor personnel may be unblinded to the treatment-level results of the interim analyses, if required, in order to act on the recommendations of the eDMC or facilitate regulatory filing after an IA. The extent to which individuals are unblinded with respect to results of IA will be documented.

The eDMC will serve as the primary reviewer of the unblinded results of the IA 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. Additional logistical details will be provided in the DMC Charter. Key aspects of the IA are described in Section 8.7.

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

PFS – RECIST 1.1 by blinded central radiologists' review

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

OS

OS is defined as the time from randomization to death due to any cause. Participants without documented death at the time of the FA will be censored at the date of the last follow-up.

Secondary

PFS – RECIST 1.1 by investigator assessment

PFS is defined as the time from randomization to the first documented disease progression or death due to any cause, whichever occurs first.

PFS – irRECIST by blinded central radiologists' review

PFS is defined as the time from randomization to the first confirmed disease progression or death due to any cause, whichever occurs first.

TTP – RECIST 1.1 by blinded central radiologists' review, and RECIST 1.1 by investigator assessment

TTP is defined as the time from randomization to the first documented disease progression. If there is no documented disease progression, TTP is censored at last tumor assessment date.

ORR – RECIST 1.1 by blinded central radiologists' review, and RECIST 1.1 by investigator assessment

ORR is defined as the proportion of the participants in the analysis population who have a CR or PR.

DOR – RECIST 1.1 by blinded central radiologists' review, and RECIST 1.1 by investigator assessment

For participants who demonstrated CR or PR, response duration is defined as the time from first documented evidence of CR or PR until disease progression or death due to any cause, whichever occurs first. Response duration for participants who have not progressed or died at the time of analysis will be censored at the date of their last tumor assessment.

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 participants will be included in this population. Participants 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 participants who received at least one dose of study treatment. Participants 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 participants this will be the treatment group to which they are randomized. Participants 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 participant 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 participant 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 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., HR) between the treatment arms. The HR and its 95% CI from the stratified Cox model with Efron's method of tie handling and with a single treatment covariate will be reported. The stratification factors used for randomization will be applied to both the stratified log-rank test and the stratified Cox model.

Since disease progression is assessed periodically, PD can occur any time in the time interval between the last assessment where PD was not documented and the assessment when PD is documented. For the primary analysis, for the participants 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. Sensitivity analyses will be performed for comparison of PFS based on investigator's assessment.

In order to evaluate the robustness of the PFS endpoint per RECIST 1.1 by blinded central radiologists' review, 2 sensitivity analyses will be performed 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 participants without documented PD or death. The censoring rules for primary and sensitivity analyses are summarized in Table 11. In case there is an imbalance between the treatment groups on disease assessment schedules or censoring patterns, the following 2 additional PFS sensitivity analyses may also be performed: 1) a PFS analysis using time to scheduled tumor assessment visit from randomization as opposed to actual tumor assessment time; 2) Finkelstein (1986)'s likelihood-based score test [38] for interval-censored data, which modifies the Cox proportional hazard model for interval-censored data, will be used as a supportive analysis for the PFS endpoint. The interval will be constructed so that the left endpoint is the date of the last disease assessment without documented PD and the right endpoint is the date of documented PD or death, whichever occurs earlier.

Table 11 Censoring rules for Primary and Sensitivity Analyses of PFS

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

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 method [39], parametric method [40], etc.

One assumption for stratified Cox proportional hazard model is that the treatment effect (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 [41], 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.

The enrollment of the study is driven by the number of PD-L1 positive participants. The enrollment will stop when approximately 360 PD-L1 positive participants are enrolled. To estimate the treatment effect in overall population with natural prevalence of PD-L1 positive and negative participants, a sensitivity analysis using the two-step weighted Cox model approach may be performed by weighting the subgroups (PD-L1 positive and PD-L1 negative) according to the natural prevalence (estimated from participants screening data) in the overall population.

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

8.6.1.2 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 HR). The HR and its 95% CI from the stratified Cox model with a single treatment covariate will be reported. The stratification factors used for will be applied to both the stratified log-rank test and the stratified Cox model.

Participants in the paclitaxel arm are expected to discontinue treatment earlier compared to participants in the pembrolizumab arm and may switch to another anti-PD-1 treatment following the verification of progressive disease by blinded central radiologists' review. Exploratory analyses to adjust for the effect of crossover (to other PD-1 therapies) on OS may be performed based on recognized methods, e.g. the Rank Preserving Structural Failure Time model proposed by Robins and Tsiatis (1989) [42], two-stage model, etc., based on an examination of the appropriateness of the data to the assumptions required by the methods.

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.

8.6.1.3 TTP

The non-parametric Kaplan-Meier method will be used to estimate the TTP curve in each treatment group. The treatment difference in TTP 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., HR) between the treatment arms. The HR and its 95% CI from the stratified Cox model with Efron's method of tie handling and with a single treatment covariate will be reported. The stratification factors used

for randomization will be applied to both the stratified log-rank test and the stratified Cox model.

8.6.1.4 ORR

Stratified Miettinen and Nurminen's method will be used for comparison of the ORRs between the treatment arms. A 95% CI for the difference in response rates between the pembrolizumab arm and paclitaxel arm will be provided. The stratification factors used for randomization will be applied to the analysis.

8.6.1.5 DOR

If sample size permits, response duration will be summarized descriptively using the Kaplan-Meier medians and quartiles. Only the subset of participants who show a CR or PRs will be included in this analysis.

Table 12 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, multiple populations, and IA is described in Section 8.7 - Interim Analyses and in Section 8.8 - Multiplicity.

Table 12 Analysis Strategy for Key Efficacy Endpoints

Endpoint/Variable (Description, Time Point)	Statistical Method†	Analysis Population	Missing Data Approach
Primary Hypothesis #1			
PFS per RECIST 1.1 by blinded central radiologists' review in PD-L1 positive participants	Test: Stratified Log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT in PD-L1 positive participants	• Primary censoring rule • Sensitivity analysis 1 • Sensitivity analysis 2 (More details are in Table 11.)
Primary Hypothesis #2			
OS in PD-L1 positive participants	Test: Stratified Log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT in PD-L1 positive participants	Censored at last known alive date
Secondary Endpoints/Hypotheses			
Secondary Hypothesis#1			
PFS per RECIST 1.1 by blinded central radiologists' review in all participants	Test: Stratified Log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT in all participants	• Primary censoring rule • Sensitivity analysis 1 • Sensitivity analysis 2 (More details are in Table 11.)
Secondary Hypothesis#2			
OS in all participants	Test: Stratified Log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT in all participants	Censored at last known alive date

Endpoint/Variable (Description, Time Point)		Statistical Method†	Analysis Population	Missing Data Approach
Other Secondary Endpoints				
PFS	per RECIST 1.1 by investigator assessment per irRECIST by blinded central radiologists' review	Test: Stratified Log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT in all below populations: • PD-L1 positive • All participants	Primary censoring rule in Table 11
TTP	per RECIST 1.1 by blinded central radiologists' review per RECIST 1.1 by investigator assessment	Test: Stratified Log-rank test Estimation: stratified Cox model with Efron's tie handling method	ITT in all below populations: • PD-L1 positive • All participants	Censored at last assessment date if no documented PD
ORR	per RECIST 1.1 by blinded central radiologists' review per RECIST 1.1 by investigator assessment	Stratified M & N method‡	ITT in all below populations: • PD-L1 positive • All participants	Participants with missing data are considered nonresponders
DOR	per RECIST 1.1 by blinded central radiologists' review per RECIST 1.1 by investigator assessment	Summary statistics using Kaplan-Meier method	All responders in ITT among all below populations: • PD-L1 positive • All participants	Censored at last assessment date if responding at the time of analysis

† Statistical models are described in further detail in the text. For stratified analyses, the stratification factors used for randomization (geographic region (Europe/Israel/North America/Australia vs. Asia vs. Rest of World), TTP on first-line therapy (< 6 months vs. ≥ 6 months) and PD-L1 status (positive vs. negative), 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 AEs, laboratory tests, vital signs, etc.

Tiered Approach

The analysis of safety results will follow a tiered approach (Table 13). The tiers differ with respect to the analyses that will be performed. Safety parameters or adverse experiences of special interest that are identified *a priori* constitute "Tier 1" safety endpoints that will be participant to inferential testing for statistical significance with p-values and 95% CIs provided for between-group comparisons. Other safety parameters will be considered Tier 2 or Tier 3. Tier 2 parameters will be assessed via point estimates with 95% CIs provided for between-group comparisons; only point estimates by treatment group are provided for Tier 3 safety parameters.

Adverse 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 participants 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% CI 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% CIs 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 participants 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% CIs (Tier 2) will be provided for between-treatment differences in the percentage of participants 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 13 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		X	X
	Specific AEs, SOCs, or PDLCs (incidence ≥4 of participants in one of the treatment groups)		X	X
Tier 3	Specific AEs, SOCs or PDLCs (incidence <4 of participants 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=Predefined Limit of Change; X = results will be provided.

Time to Grade 3-5 AE

In addition to tiered approach, exploratory analysis will be performed on time to first Grade 3-5 AE. Time to first Grade 3-5 AE is defined as the time from the first day of study drug to the first event of Grade 3-5 AE. The Kaplan-Meier method will be used to estimate the curve of time to first Grade 3-5 AE. The treatment difference in time to first Grade 3-5 AE will be assessed by the log-rank test. A 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 HR). The HR and its 95% CI from the Cox model with a single treatment covariate will be reported. See details in sSAP.

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 participants 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 one planned IA in this trial. Results will be reviewed by an eDMC.

The primary purpose of the IA is to evaluate superiority of pembrolizumab in OS and PFS. It will be performed after: (1) enrollment is completed; (2) approximately 240 OS events have been observed among PD-L1 positive participants; and 3) a minimum of 260 PFS events have been observed among PD-L1 positive participants.

For the PFS hypothesis, the boundary to demonstrate PFS superiority is shown in

Table 14 which corresponds to an approximate observed HR of 0.74 or less at IA at α = 0.35% (one-sided), if 320 PFS events are analyzed at this time.

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 information fraction of the number of OS events observed at the time of the IA over 290 events, using the alpha-spending function.

If the time from the IA to the FA is estimated to increase (e.g., 16 months after IA), adding an additional IA approximately 1 year after the first IA may be considered. In this case, the boundaries for the additional IA and FA will be adjusted, but the alpha-spending function with gamma parameter (-4) remains unchanged during the course of trial. The overall type-I error control is not affected.

In order to account for potential delayed treatment effect, which was observed with immunotherapy study data external to this study, the FA will be at least 290 OS events among the PD-L1 positive participants or approximately 15 months after last patient randomized, whichever is later [43] [44] [45]. The additional follow-up time is incorporated into the trial to ensure that the FA is conducted at an appropriate time to characterize the potential benefit of immunotherapy, where the treatment effect is most pronounced toward the tail of the survival curve. The boundary for the FA will be adjusted according to the actual alpha spent at IA and the actual number of events at IA and FA.

Table 14 summarizes the timing, sample size and decision guidance of the IA and FA. Bounds are based on estimated number of events and will be updated at times of analyses using spending functions as noted above.

Table 14 Summary of Timing, Sample Size and Decision Guidance of Interim Analysis and Final Analysis

Analysis	Criteria for Conduct of Analysis	Endpoint	Value	Efficacy	Futility
Interim Analysis: Interim OS Analysis /Main PFS Analysis	(1) enrollment is complete (2) approximately 240 OS events have been observed among PD-L1 positive participants 3) a minimum of 260 PFS events have been observed among PD-L1 positive participants PFS Events among PD-L1 positive participants: ~320 OS Events among PD-L1 positive participants: ~240	PFS in PD-L1 positive participants	p value (1-sided) at boundary	<=0.0035	NA
			~ HR at boundary	0.74	NA
		OS in PD-L1 positive participants	p value (1-sided) at boundary	<=0.0107	NA
			~ HR at boundary	0.74	NA
Final Analysis: Main OS Analysis	At least 290 OS events have been observed among PD-L1 positive participants, or approximately 15 months after last patient randomized, whichever is later. OS Events among PD-L1 positive participants: ~290	OS in PD-L1 positive participants	p value (1-sided) at boundary	<=0.0187	NA
			~ HR at boundary	0.78	NA

8.8 Multiplicity

The multiplicity strategy specified in this section will be applied to the 2 primary hypotheses (superiority of pembrolizumab on PFS or OS in PD-L1 positive participants) and the 2 secondary hypotheses (superiority of pembrolizumab on PFS or OS in all participants).

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.

For OS, the Type-I error rate for the IA and FA is controlled through alpha-spending functions for the PD-L1 positive population as described in Section 8.7 - Interim Analyses. For the overall population at IA, the same alpha level allocated to the PD-L1 positive population at IA will be used. For the overall population at FA, the alpha level will be calculated based on the total alpha for the OS endpoint, alpha used at IA, and actual number of events at IA and FA.

Within each endpoint at IA and FA, the Type-I error rate for hypotheses on different populations will then be controlled by step-down method (PD-L1 positive participants first and then the all participants).

If pembrolizumab arm demonstrates superior PFS in both PD-L1 positive participants and all participants, then the corresponding alpha level can be shifted to the hypotheses for the OS endpoint using the graphical approach of Maurer and Bretz (2013) [37].

See Figure 2 for the multiplicity strategy diagram of the study.

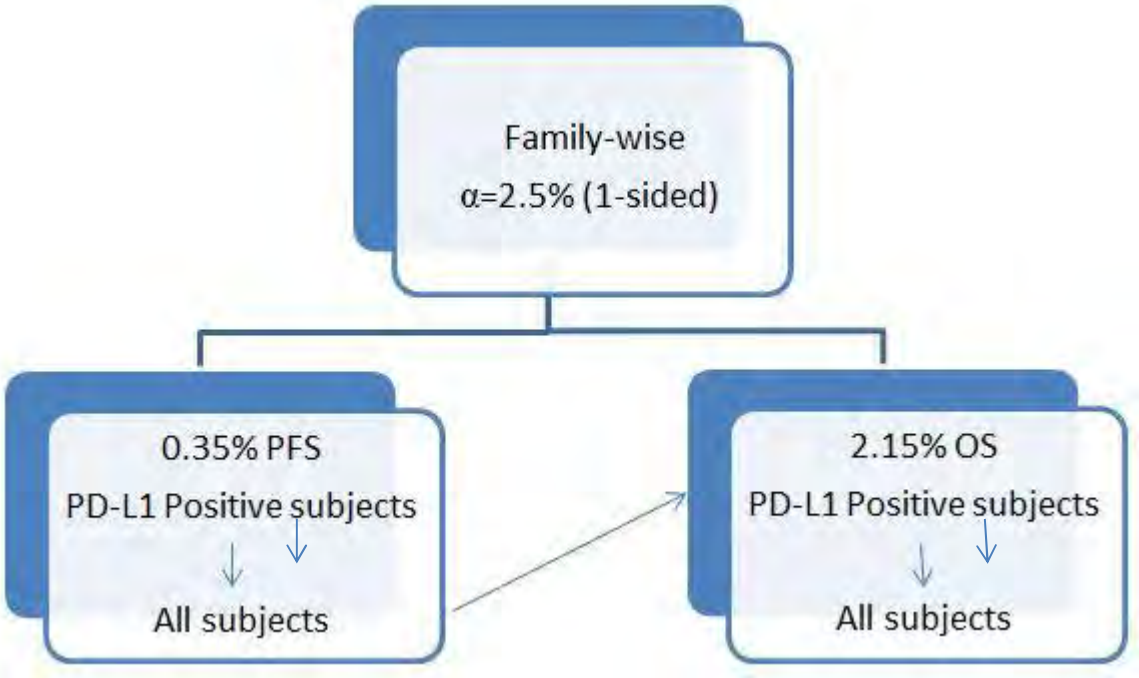


Figure 2 Multiplicity Strategy

8.9 Sample Size and Power Calculations

The study will randomize participants in a 1:1 ratio into pembrolizumab arm and paclitaxel arm. The overall sample size will be up to approximately 720 (~360 PD-L1 positive participants and up to approximately 360 PD-L1 negative participants). That is, enrollment of the PD-L1 negative participants will be stopped, either when 360 PD-L1 positive participants have been enrolled or when 360 PD-L1 negative participants have been enrolled, whichever comes first. However, participants already in screening phase may be enrolled even after the maximum sample size has been reached.

Based on recommendations from an eDMC, PD-L1 negative participants are no longer eligible for enrollment into the study as of 20-MAR-2016; however, all participants enrolled prior to 20-MAR-2016 may continue on the study regardless of PD-L1 status. Therefore, as of 20-MAR-2016, enrollment will only include those participants with PD-L1 positive expressions on their tumor. This enrollment change does not impact the statistical analysis plan. Enrollment was completed on 27-JUL-2016.

The FA of the study will complete after at least 290 OS events have been observed in the PD-L1 positive participants, or approximately 15 months after last patient randomized, whichever is later.

PFS analysis: As described in Section 8.7 - Interim Analyses, the main PFS analysis will be carried out at the IA. Approximately 320 PFS events will be accumulated in the positive PD-L1 participants at that time. An alpha of 0.35% will be allocated to PFS in the positive participants at this analysis. With ~320 PFS events in the PD-L1 positive participants, this IA has 99% (97%) power to demonstrate that pembrolizumab is superior to paclitaxel at a one-

sided 0.35% alpha-level, if the underlying HR of PFS is 0.5 (0.6). Success for PFS at the main analysis approximately corresponds to an observed HR of <0.74.

The power calculation is based on the following assumptions for participants in the positive PD-L1 population: 1) PFS follows an exponential distribution with a median of 3 months in the paclitaxel arm; 2) An enrollment period of 14 months (IA is conducted when enrollment is complete); 3) A yearly dropout rate of 5%.

OS analysis: The final OS analysis will be carried out when at least **290** OS events have occurred in the PD-L1 positive participants, or approximately 15 months after last patient randomized, whichever is later. For primary endpoint OS in the PD-L1 positive participants, the trial has 91% (85%) power to demonstrate that pembrolizumab is superior to paclitaxel at a one-sided 2.15% alpha-level, if the underlying HR of OS is 0.67 (0.7) and 290 OS events are observed. Success for OS at the FA approximately corresponds to an observed HR of <0.78 (approximately a 2-month improvement or greater in median OS).

The sample size and power calculation are based on the following assumptions for participants in the positive PD-L1 population: 1) OS follows an exponential distribution with a median of 7.5 months in the control arm; 2) An enrollment period of 14 months; 3) A yearly dropout rate of 2%.

The assumptions for the median PFS of 3 months and the median OS of 7.5 months in the paclitaxel arm are based on estimates of median PFS and median OS from RAINBOW trial [30].

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)
- Geographic region (Europe/Israel/North America/Australia vs. Asia vs. Rest of World)
- Ethnic origin (Hispanic vs. Non-Hispanic)
- PD-L1 (Positive vs. Negative)
- ECOG PS (0 vs. 1)
- Primary location (Stomach vs. GEJ)
- Histological subtype (Diffuse vs. intestinal vs. mixed)
- Disease Status (Locally advanced vs. Metastatic)
- TTP on first-line therapy (< 6 months vs. ≥ 6 months)

8.11 Compliance (Medication Adherence)

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

8.12 Extent of Exposure

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

9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.1 Investigational Product

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

Clinical Supplies will be provided by the Sponsor as summarized in Table 15.

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 15 Product Descriptions

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

All supplies indicated in Table 15 will be provided per the "Source/Additional Information" column depending on local country operational requirements.

Any commercially available product not included in Table 15 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.

Participants 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

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

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

10.1 Confidentiality

10.1.1 Confidentiality of Data

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

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

10.1.2 Confidentiality of Subject Records

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

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

10.1.3 Confidentiality of Investigator Information

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

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

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

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

10.1.4 Confidentiality of IRB/IEC Information

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

10.2 Compliance with Financial Disclosure Requirements

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

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

10.3 Compliance with Law, Audit and Debarment

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

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

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

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

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

Trial documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the trial site upon request for inspection, copying, review and audit at reasonable times by representatives of the Sponsor or any regulatory authorities. The investigator agrees to promptly take any reasonable steps that are

requested by the Sponsor as a result of an audit to cure deficiencies in the trial documentation and worksheets/case report forms.

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

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

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

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

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

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

individual to serve as the Protocol CI and or CSR CI (e.g., availability of the CI during the anticipated review process, thorough understanding of clinical trial methods, appropriate enrollment of subject cohort, timely achievement of trial milestones). The Protocol CI must be a participating trial investigator.

10.4 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Amendments Act (FDAAA) of 2007, and the European Medicines Agency (EMA) clinical trial Directive 2001/20/EC, the Sponsor of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to http://www.clinicaltrials.gov, www.clinicaltrialregister.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 trials 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.

11.0 LIST OF REFERENCES

[1] Disis ML. Immune regulation of cancer. J Clin Oncol 2010;28(29):4531-8.

[2] Dong H, Strome SE, Salomao DR, Tamura H, Hirano F, Flies DB, et al. Tumor-associated B7-H1 promotes T-cell apoptosis: a potential mechanism of immune evasion. Nat Med 2002;8(8):793-800.

[3] Sharpe AH, Freeman GJ. The B7-CD28 superfamily. Nat Rev Immunol 2002;2(2):116-26.

[4] Brown JA, Dorfman DM, Ma F-R, Sullivan EL, Munoz O, Wood CR, et al. Blockade of programmed death-1 ligands on dendritic cells enhances T cell activation and cytokine production. J Immunol 2003;170(3):1257-66.

[5] Francisco LM, Sage PT, Sharpe AH. The PD-1 pathway in tolerance and autoimmunity. Immunol Rev 2010;236:219-42.

[6] Thompson RH, Dong H, Lohse CM, Leibovich BC, Blute ML, Cheville JC, et al. PD-1 is expressed by tumor-infiltrating immune cells and is associated with poor outcome for patients with renal cell carcinoma. Clin Cancer Res 2007;13(6):1757-61.

[7] Talmadge JE, Donkor M, Scholar E. Inflammatory cell infiltration of tumors: Jekyll or Hyde. Cancer Metastasis Rev 2007;26(3-4):373-400.

[8] Usubütün A, Ayhan A, Uygur MC, Özen H, Toklu C, Ruacan S. Prognostic factors in renal cell carcinoma. J Exp Clin Cancer Res 1998;17(1):77-81.

[9] Al-Shibli KI, Donnem T, Al-Saad S, Persson M, Bremnes RM, Busund L-T. Prognostic effect of epithelial and stromal lymphocyte infiltration in non-small cell lung cancer. Clin Cancer Res 2008;14(16):5220-7.

[10] Deschoolmeester V, Baay M, Van Marck E, Weyler J, Vermeulen P, Lardon F, et al. Tumor infiltrating lymphocytes: an intriguing player in the survival of colorectal cancer patients. BMC Immunol. 2010 Apr 12;11:19.

[11] Diez M, Pollán M, Enriquez JM, Dominguez P, Santana A, Tobaruela E, et al. Histopathologic prognostic score in colorectal adenocarcinomas. Anticancer Res 1998;18(1B):689-94.

[12] Galon J, Costes A, Sanchez-Cabo F, Kirilovsky A, Mlecnik B, Lagorce-Pagès C, et al. Type, density, and location of immune cells within human colorectal tumors predict clinical outcome. Science 2006;313(5795):1960-4.

[13] Hiraoka N. Tumor-infiltrating lymphocytes and hepatocellular carcinoma: molecular biology. Int J Clin Oncol 2010;15(6):544-51.

[14] Nobili C, Degrate L, Caprotti R, Franciosi C, Leone BE, Trezzi R, et al. Prolonged survival of a patient affected by pancreatic adenocarcinoma with massive lymphocyte and dendritic cell infiltration after interleukin-2 immunotherapy. Report of a case. Tumori 2008;94(3):426-30.

[15] Hodi FS, Dranoff G. The biologic importance of tumor-infiltrating lymphocytes. J Cutan Pathol 2010;37(Suppl 1):48-53.

[16] Kloor M. Lymphocyte infiltration and prognosis in colorectal cancer. Lancet Oncol. 2009 Sep;10(9):840-1.

[17] Hillen F, Baeten CIM, van de Winkel A, Creytens D, van der Schaft DWJ, Winnepenninckx V, et al. Leukocyte infiltration and tumor cell plasticity are parameters of aggressiveness in primary cutaneous melanoma. Cancer Immunol Immunother 2008;57(1):97-106.

[18] Lee HE, Chae SW, Lee YJ, Kim MA, Lee HS, Lee BL, et al. Prognostic implications of type and density of tumour-infiltrating lymphocytes in gastric cancer. Br J Cancer 2008;99(10):1704-11.

[19] Leffers N, Gooden MJM, de Jong RA, Hoogeboom B-N, ten Hoor KA, Hollema H, et al. Prognostic significance of tumor-infiltrating T-lymphocytes in primary and metastatic lesions of advanced stage ovarian cancer. Cancer Immunol Immunother 2009;58(3):449-59.

[20] Nishimura H, Honjo T, Minato N. Facilitation of beta selection and modification of positive selection in the thymus of PD-1-deficient mice. J Exp Med. 2000 Mar 6;191(5):891-8.

[21] Liotta F, Gacci M, Frosali F, Querci V, Vittori G, Lapini A, et al. Frequency of regulatory T cells in peripheral blood and in tumour-infiltrating lymphocytes correlates with poor prognosis in renal cell carcinoma. BJU Int 2011;107(9):1500-6.

[22] Cancer Genome Atlas Research Network. Comprehensive molecular characterization of gastric adenocarcinoma. Nature. 2014 Sep 11;513(7517):202-9.

[23] Ropponen KM, Eskelinen MJ, Lipponen PK, Alhava E, Kosma V-M. Prognostic value of tumour-infiltrating lymphocytes (TILs) in colorectal cancer. J Pathol 1997;182(3):318-24.

[24] Dudley ME, Wunderlich JR, Yang JC, Sherry RM, Topalian SL, Restifo NP, et al. Adoptive cell transfer therapy following non-myeloablative but lymphodepleting chemotherapy for the treatment of patients with refractory metastatic melanoma. J Clin Oncol 2005;23(10):2346-57.

[25] Hunder NN, Wallen H, Cao J, Hendricks DW, Reilly JZ, Rodmyre R, et al. Treatment of metastatic melanoma with autologous CD4+ T cells against NY-ESO-1. N Engl J Med. 2008 Jun 19;358(25):2698-703.

[26] Pölcher M, Braun M, Friedrichs N, Rudlowski C, Bercht E, Fimmers R, et al. Foxp3(+) cell infiltration and granzyme B(+)/Foxp3(+) cell ratio are associated with outcome in neoadjuvant chemotherapy-treated ovarian carcinoma. Cancer Immunol Immunother 2010;59(6):909-19.

[27] Okazaki T, Maeda A, Nishimura H, Kurosaki T, Honjo T. PD-1 immunoreceptor inhibits B cell receptor-mediated signaling by recruiting src homology 2-domain-containing tyrosine phosphatase 2 to phosphotyrosine. Proc Natl Acad Sci U S A 2001;98(24):13866-71.

[28] Greenwald RJ, Freeman GJ, Sharpe AH. The B7 family revisited. Annu Rev Immunol 2005;23:515-48.

[29] Muro K, Bang Y, Shankaran V, Geva R, Catenacci DV, Gupta S, et al. LBA15 - A phase 1b study of pembrolizumab (Pembro; MK-3475) in patients (Pts) with advanced gastric cancer. European Society for Medical Oncology (ESMO); 2014 Sep 26-30; Madrid, ES.

[30] Wilke H, Muro K, Van Cutsem E, Oh SC, Bodoky G, Shimada Y, et al. Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): a double-blind, randomised phase 3 trial. Lancet Oncol. 2014 Oct;15(11):1224-35.

[31] Fuchs CS, Tomasek J, Yong CJ, Dumitru F, Passalacqua R, Goswami C, et al. Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): an international, randomised, multicentre, placebo-controlled, phase 3 trial. Lancet. 2014 Jan 4;383(9911):31-9.

[32] Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 1993;85(5):365-76.

[33] EuroQol Group. EuroQol - a new facility for the measurement of health-related quality of life. Health Policy. 1990 Dec;16(3):199-208.

[34] Rizzo JD, Somerfield MR, Hagerty KL, Seidenfeld J, Bohlius J, Bennett CL, et al. Use of epoetin and darbepoetin in patients with cancer: 2007 American Society of Clinical Oncology/American Society of Hematology clinical practice guideline update. J Clin Oncol 2008;26(1):132-49.

[35] National Comprehensive Cancer Network. Cancer- and chemotherapy- induced anemia, 2014.

[36] Miettinen O, Nurminen M. Comparative analysis of two rates. Stat Med 1985;4:213-26.

[37] Maurer W, Bretz F. Multiple testing in group sequential trials using graphical approaches. Stat Biopharm Res 2013;5(4):311-20.

[38] Finkelstein DM. A proportional hazards model for interval-censored failure time data. Biometrics 1986;42:845-54.

[39] Uno H, Claggett B, Tian L, Inoue E, Gallo P, Miyata T, et al. Moving beyond the hazard ratio in quantifying the between-group difference in survival analysis. J Clin Oncol. 2014 Aug 1;32(22):2380-5.

[40] Odell PM, Anderson KM, Kannel WB. New models for predicting cardiovascular events. J Clin Epidemiol. 1994 Jun;47(6):583-92.

[41] Mehrotra DV, Su SC, Li X. An efficient alternative to the stratified Cox model analysis. Stat Med. 2012 Jul 30;31(17):1849-56.

[42] Robins JM, Tsiatis AA. Correcting for non-compliance in randomized trials using rank preserving structural failure time models. Commun Stat-Theor M 1991;20(8):2609-31.

[43] Ferris RL, Blumenschein G Jr, Fayette J, Guigay J, Colevas AD, Licitra L, et al. Nivolumab for Recurrent Squamous-Cell Carcinoma of the Head and Neck. N Engl J Med. 2016 Nov 10;375(19):1856-1867.

[44] Borghaei H, Paz-Ares L, Horn L, Spigel DR, Steins M, Ready NE, et al. Nivolumab versus Docetaxel in Advanced Nonsquamous Non-Small-Cell Lung Cancer. N Engl J Med. 2015 Oct 22;373(17):1627-39.

[45] Bellmunt J, de Wit R, Vaughn DJ, Fradet Y, Lee JL, Fong L, et al. Pembrolizumab as Second-Line Therapy for Advanced Urothelial Carcinoma. N Engl J Med. 2017 Mar 16;376(11):1015-1026.

12.0 APPENDICES

12.1 Merck Code of Conduct for Clinical Trials

Merck*
Code of Conduct for Clinical Trials

I. Introduction

A. Purpose

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

B. Scope

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

II. Scientific Issues

A. Trial Conduct

1. Trial Design

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

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

2. Site Selection

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

3. Site Monitoring/Scientific Integrity

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

B. Publication and Authorship

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

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

III. Subject Protection

A. IRB/ERC review

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

B. Safety

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

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

C. Confidentiality

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

D. Genomic Research

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

IV. Financial Considerations

A. Payments to Investigators

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

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

B. Clinical Research Funding

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

C. Funding for Travel and Other Requests

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

V. Investigator Commitment

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

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

12.2 Collection and Management of Specimens for Future Biomedical Research

1. Definitions

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

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

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

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research

The specimens collected in this trial as outlined in Section 7.1.3.5 – Future Biomedical Research will be used to study various causes for how subjects may respond to a drug/vaccine. Future biomedical research specimen(s) will be stored to provide a resource for future trials conducted by Merck focused on the study of biomarkers responsible for how a drug/vaccine enters and is removed by the body, how a drug/vaccine works, other pathways a drug/vaccine may interact with, or other aspects of disease. The specimen(s) may be used for future assay development and/or drug/vaccine development.

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

3. Summary of Procedures for Future Biomedical Research

a. Subjects for Enrollment

All subjects enrolled in the clinical trial will be considered for enrollment in 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 Visit 1. If delayed, present consent at next possible Subject Visit. Informed consent must be obtained prior to collection of all Future Biomedical Research specimens. Consent forms signed by the subject will be kept at the clinical trial site under secure storage for regulatory reasons. Information contained on the consent form alone cannot be traced

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

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

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

c. eCRF Documentation for Future Biomedical Research Specimens

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

d. Future Biomedical Research Specimen Collections

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

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

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

4. Confidential Subject Information for Future Biomedical Research

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

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

At the clinical trial site, unique codes will be placed on the Future Biomedical Research specimens for transfer to the storage facility. This first code is a random number which

does not contain any personally identifying information embedded within it. The link (or key) between subject identifiers and this first unique code will be held at the trial site. No personal identifiers will appear on the specimen tube.

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

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

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

5. Biorepository Specimen Usage

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

Analyses utilizing the Future Biomedical Research specimens may be performed by Merck, or an additional third party (e.g., a university investigator) designated by Merck. The investigator conducting the analysis will be provided with double coded specimens. Re-association of analysis results with corresponding clinical data will only be conducted by the Merck Entrusted Keyholder. Any contracted third party analyses will conform to the specific scope of analysis outlined in future biomedical research protocol and consent. Future Biomedical Research specimens remaining with the third party after the specific analysis is performed will be returned to the sponsor or destroyed and documentation of destruction will be reported to Merck.

6. Withdrawal From Future Biomedical Research

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

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

7. Retention of Specimens

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

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

8. Data Security

Separate databases for specimen information and for results from the Future Biomedical Research sub-trial will be maintained by Merck. This is done to separate the future exploratory test results (which include genetic data) from the clinical trial database thereby maintaining a separation of subject number and these results. The separate databases are accessible only to the authorized Sponsor and the designated trial administrator research personnel and/or collaborators. Database user authentication is highly secure, and is accomplished using network security policies and practices based in international standards (e.g., ISO17799) to protect against unauthorized access. The Merck Entrusted Keyholder maintains control over access to all specimen data. These data are collected for future biomedical research purposes only as specified in this sub-trial will not be used for any other purpose.

9. Reporting of Future Biomedical Research Data to Subjects

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

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

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

10. Gender, Ethnicity and Minorities

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

11. Risks Versus Benefits of Future Biomedical Research

For future biomedical research, risks to the participant have been minimized. No additional risks to the participant 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.

12. Self-Reported Ethnicity

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

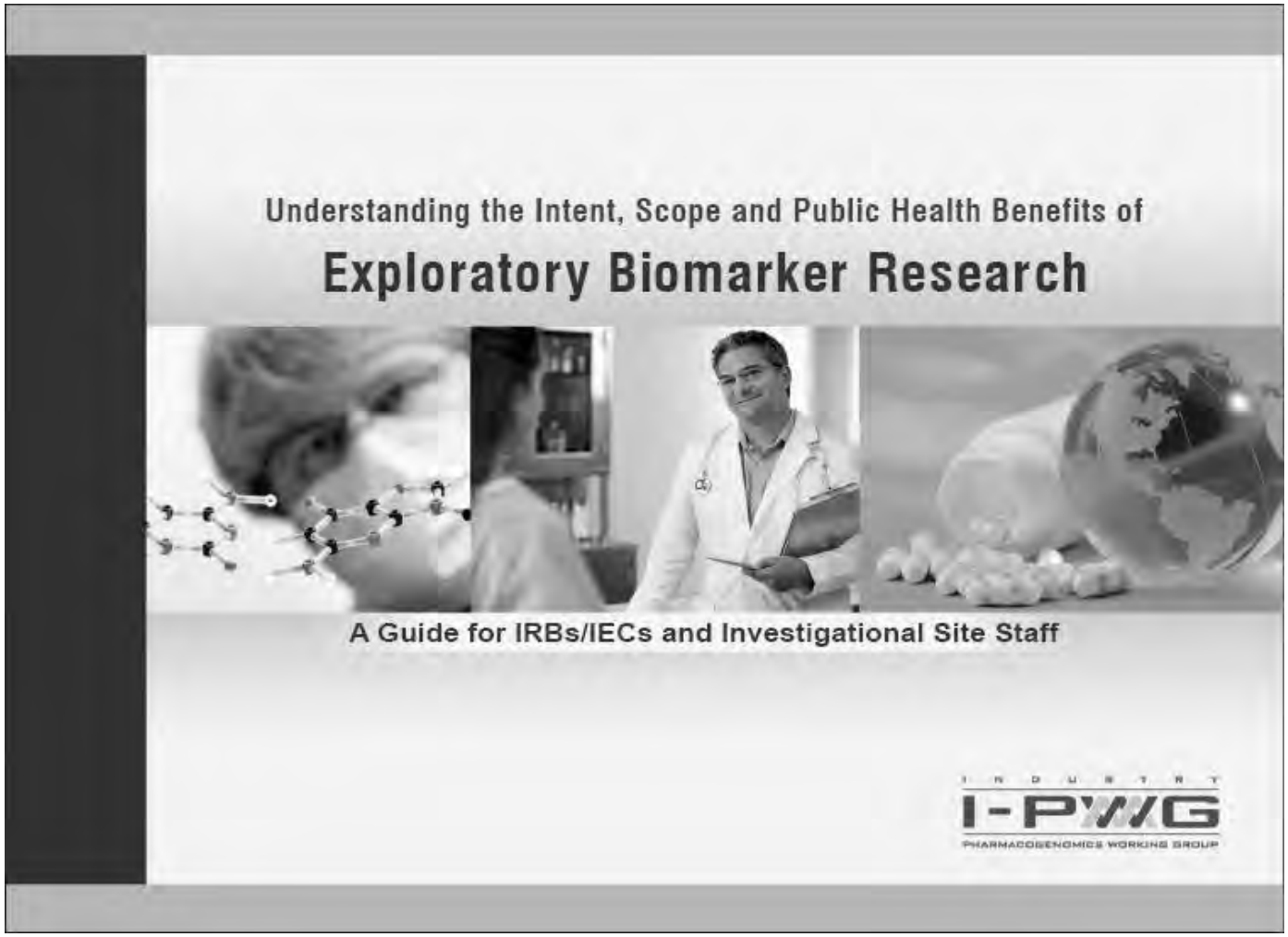
13. Questions

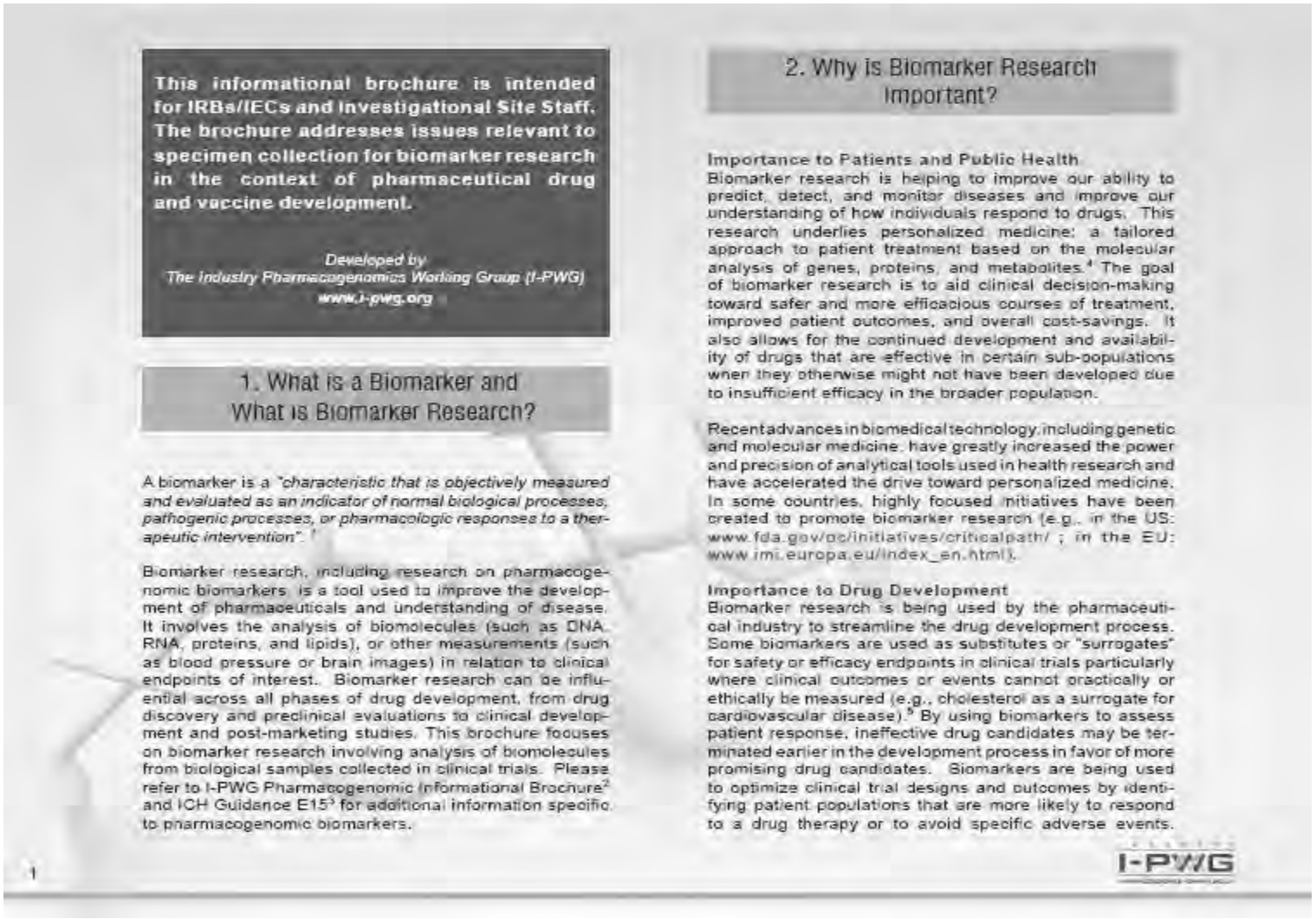
Any questions related to the future biomedical research should be e-mailed directly to clinical.specimen.management@merck.com.

14. References

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

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





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

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

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

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

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

2. Why is Biomarker Research Important?

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

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

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

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

3. Importance of Biomarkers to Regulatory Authorities

Regulatory health authorities are increasingly aware of the benefits of biomarkers and how they may be used for drug approval, clinical trial design, and clinical care. Biomarkers have been used to establish risk:benefit profiles. For example, the FDA has modified the US warfarin (Coumadin®) label to include the analysis of *CYP2C9* and *VKORC1* genes to guide dosing regimens. Health authorities such as the FDA (USA), EMEA (European Union), MHLW (Japan), and ICH (International) are playing a key role in advancing this scientific field as it applies to pharmaceutical development by creating the regulatory infrastructure to facilitate this research. Numerous regulatory guidances and concept papers have already been issued, many of which are available through www.i-pwg.org. Global regulatory authorities have highlighted the importance of biomarker research and the need for the pharmaceutical industry to take the lead in this arena.[3,5-24]

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

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

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

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

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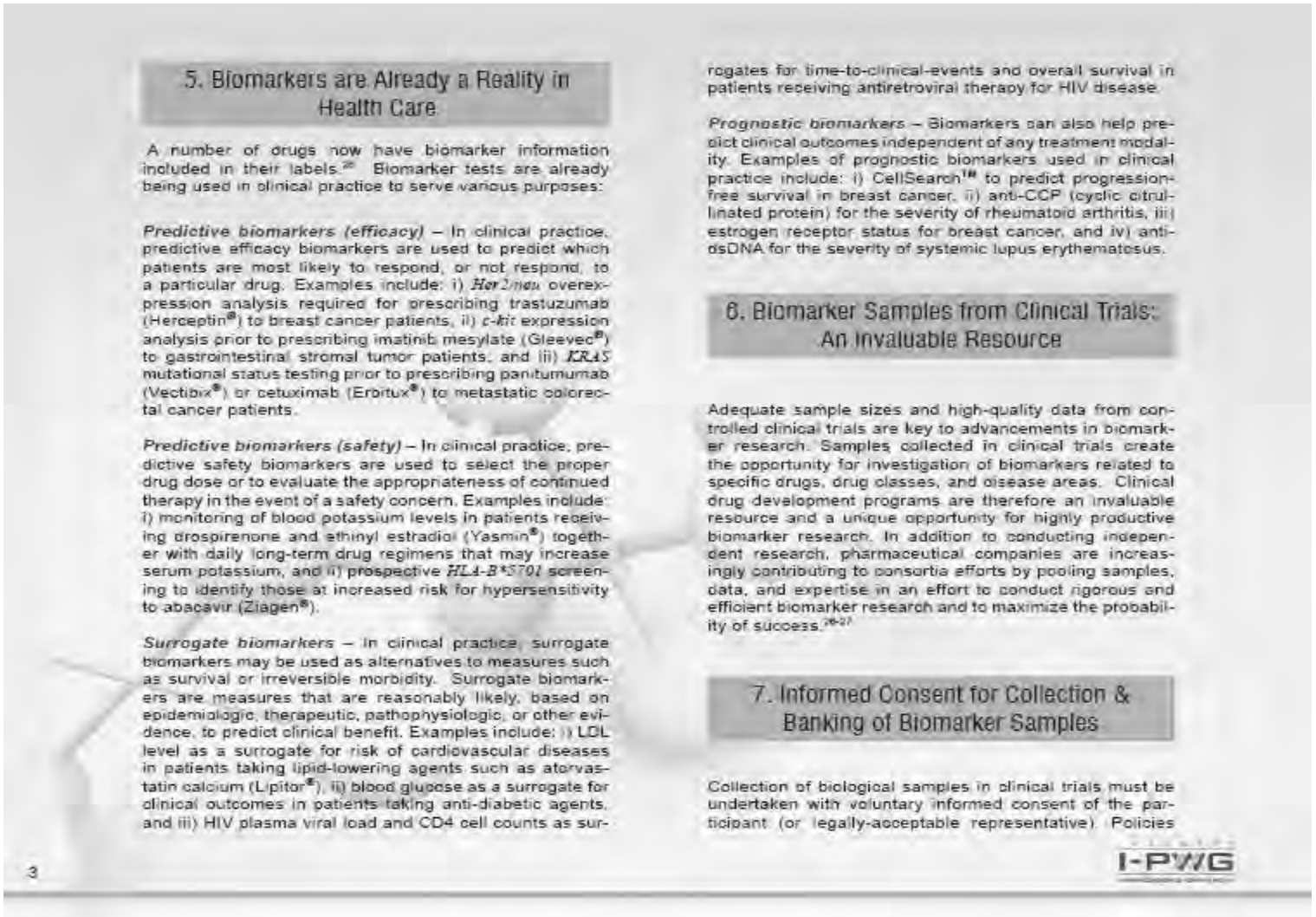

5. Biomarkers are Already a Reality in Health Care

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

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

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

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

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

6. Biomarker Samples from Clinical Trials: An Invaluable Resource

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

7. Informed Consent for Collection & Banking of Biomarker Samples

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

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

Optional vs. Required Subject Participation

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

Consent for Future Research Use

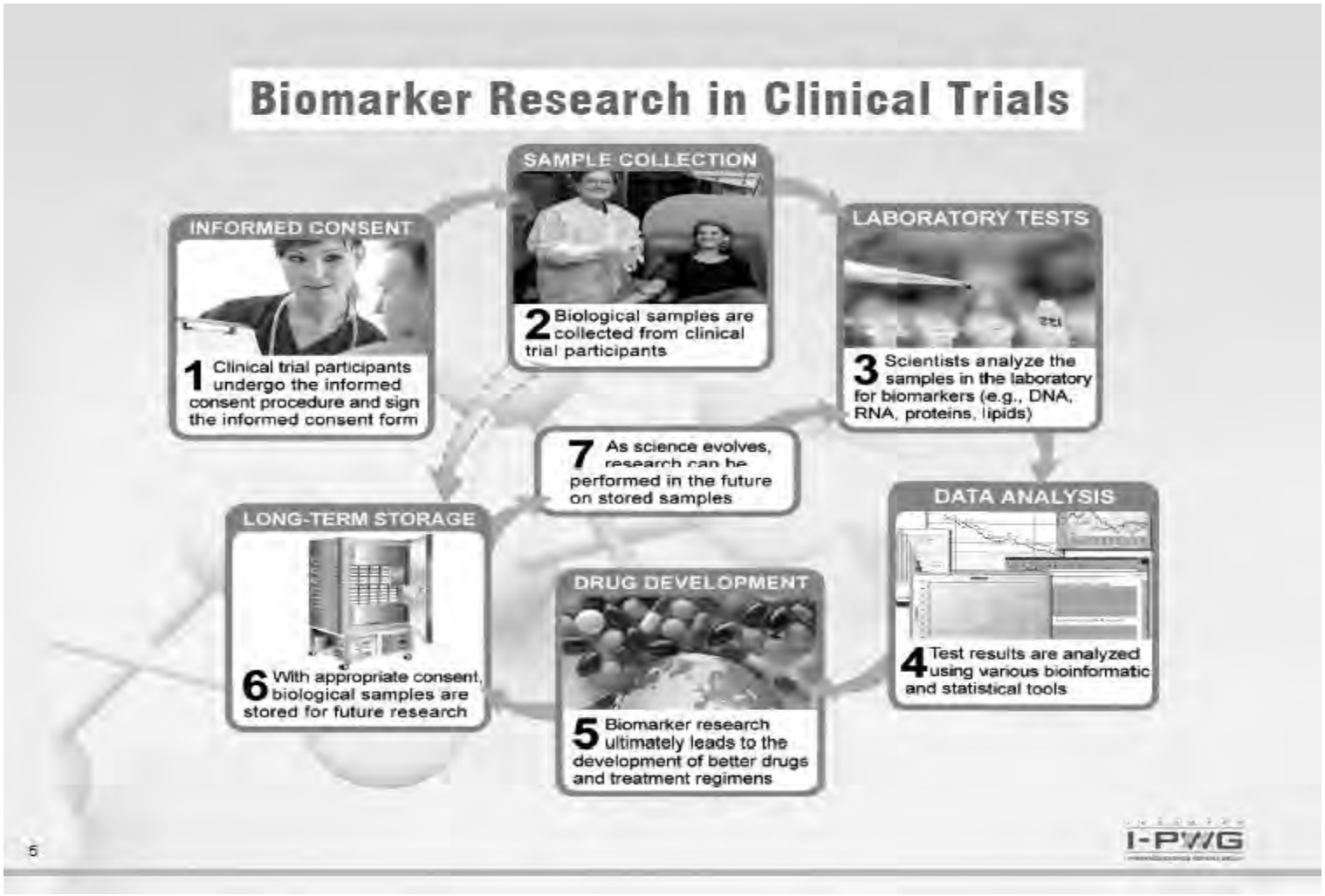
While it can be a challenge to specify the details of the research that will be conducted in the future, the I-PWG holds the view that future use of samples collected for exploratory biomarker research in clinical trials should be permissible when i) the research is scientifically sound, ii) participants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

Important elements of informed consent for **future use** of samples include, but are not limited to:[29]

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.[31]

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


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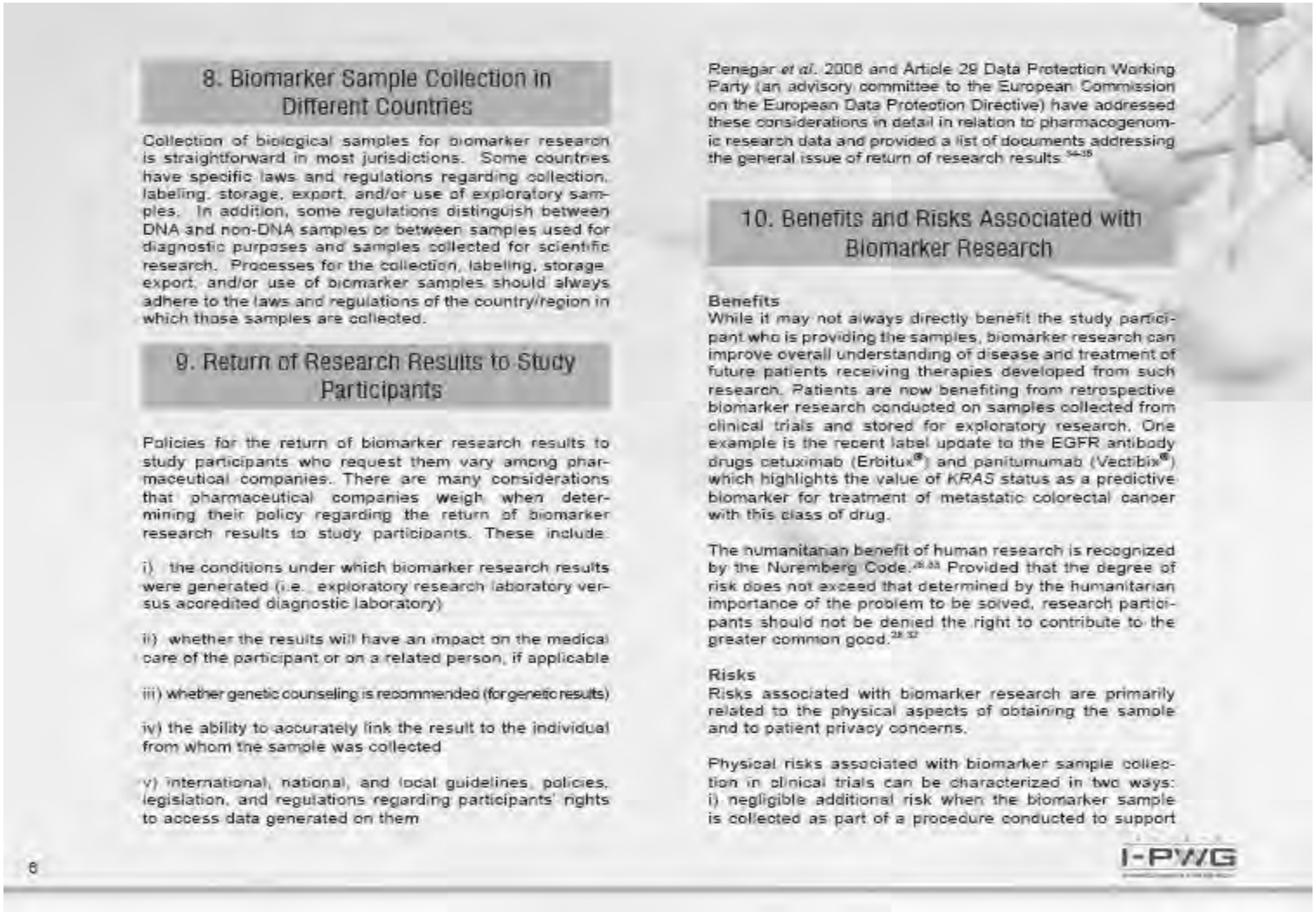

8. Biomarker Sample Collection in Different Countries

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

9. Return of Research Results to Study Participants

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

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

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

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

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

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

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

10. Benefits and Risks Associated with Biomarker Research

Benefits

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

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

Risks

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

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

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

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

11. Privacy, Confidentiality, and Patient Rights

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

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

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

This standard dictates that *"the confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with applicable regulatory requirements."* [21]

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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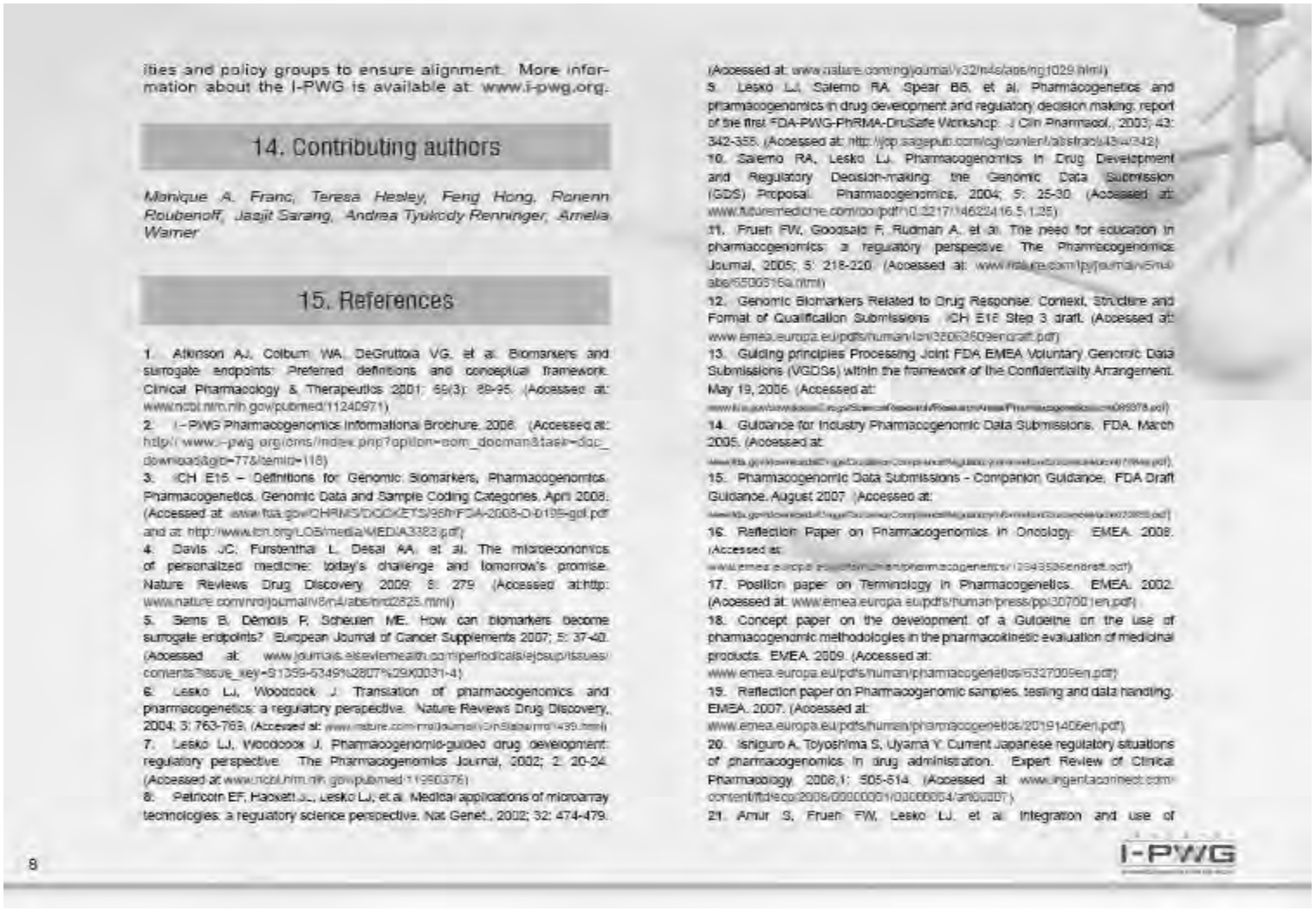

ities and policy groups to ensure alignment. More information about the I-PWG is available at: www.i-pwg.org.

14. Contributing authors

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15. References

1. Atkinson AJ, Colburn WA, DeGruttola VG, et al. Biomarkers and surrogate endpoints: Preferred definitions and conceptual framework. Clinical Pharmacology & Therapeutics 2001; 69(3): 89-95. (Accessed at: www.ncbi.nlm.nih.gov/pubmed/11240971)
2. I-PWG Pharmacogenomics Informational Brochure. 2006. (Accessed at: http://www.i-pwg.org/cms/index.php?option=com_docman&task=doc_download&gid=77&Itemid=118)
3. ICH E15 – Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories. April 2008. (Accessed at: www.fda.gov/OHRMS/DOCKETS/98fr/FDA-2008-D-0195-gdl.pdf and at: http://www.ich.org/LOB/media/MEDIA3383.pdf)
4. Davis JC, Furstenthal L, Desai AA, et al. The microeconomics of personalized medicine: today's challenge and tomorrow's promise. Nature Reviews Drug Discovery 2009; 8: 279. (Accessed at:http://www.nature.com/nrd/journal/v8/n4/abs/nrd2825.html)
5. Sems B, Démolis P, Scheulen ME. How can biomarkers become surrogate endpoints? European Journal of Cancer Supplements 2007; 5: 37-40. (Accessed at: www.journals.elsevierhealth.com/periodicals/ejcsup/issues/contents?issue_key=S1359-6349%2807%29X0031-4)
6. Lesko LJ, Woodcock J. Translation of pharmacogenomics and pharmacogenetics: a regulatory perspective. Nature Reviews Drug Discovery, 2004; 3: 763-769. (Accessed at: www.nature.com/nrd/journal/v3/n9/abs/nrd1499.html)
7. Lesko LJ, Woodcock J. Pharmacogenomic-guided drug development: regulatory perspective. The Pharmacogenomics Journal, 2002; 2: 20-24. (Accessed at:www.ncbi.nlm.nih.gov/pubmed/11990376)
8. Petricoin EF, Hackett JL, Lesko LJ, et al. Medical applications of microarray technologies: a regulatory science perspective. Nat Genet., 2002; 32: 474-479. (Accessed at: www.nature.com/ng/journal/v32/n4s/abs/ng1029.html)
9. Lesko LJ, Salerno RA, Spear BB, et al. Pharmacogenetics and pharmacogenomics in drug development and regulatory decision making: report of the first FDA-PWG-PhRMA-DruSafe Workshop. J Clin Pharmacol., 2003; 43: 342-355. (Accessed at: http://jcp.sagepub.com/cgi/content/abstract/43/4/342)
10. Salerno RA, Lesko LJ. Pharmacogenomics in Drug Development and Regulatory Decision-making: the Genomic Data Submission (GDS) Proposal. Pharmacogenomics, 2004; 5: 25-30. (Accessed at: www.futuremedicine.com/doi/pdf/10.2217/14622416.5.1.25)
11. Frueh FW, Goodsaid F, Rudman A, et al. The need for education in pharmacogenomics: a regulatory perspective. The Pharmacogenomics Journal, 2005; 5: 218-220. (Accessed at: www.nature.com/tpj/journal/v5/n4/abs/5500316a.html)
12. Genomic Biomarkers Related to Drug Response: Context, Structure and Format of Qualification Submissions. ICH E16 Step 3 draft. (Accessed at: www.emea.europa.eu/pdfs/human/ich/3206209encraft.pdf)
13. Guiding principles Processing Joint FDA EMEA Voluntary Genomic Data Submissions (VGDSs) within the framework of the Confidentiality Arrangement. May 19, 2006. (Accessed at:
14. Guidance for Industry Pharmacogenomic Data Submissions. FDA. March 2005. (Accessed at:
15. Pharmacogenomic Data Submissions - Companion Guidance. FDA Draft Guidance. August 2007. (Accessed at:
16. Reflection Paper on Pharmacogenomics in Oncology. EMEA. 2008. (Accessed at:
17. Position paper on Terminology in Pharmacogenetics. EMEA. 2002. (Accessed at: www.emea.europa.eu/pdfs/human/press/pp/30700 1en.pdf)
18. Concept paper on the development of a Guideline on the use of pharmacogenomic methodologies in the pharmacokinetic evaluation of medicinal products. EMEA. 2009. (Accessed at: www.emea.europa.eu/pdfs/human/pharmacogenetics/6327009en.pdf)
19. Reflection paper on Pharmacogenomic samples, testing and data handling. EMEA. 2007. (Accessed at: www.emea.europa.eu/pdfs/human/pharmacogenetics/20191406en.pdf)
20. Ishiguro A, Toyoshima S, Uyama Y. Current Japanese regulatory situations of pharmacogenomics in drug administration. Expert Review of Clinical Pharmacology. 2008;1: 505-514. (Accessed at: www.ingentaconnect.com/content/ftd/ecp/2008/00000001/00000004/art00007)
21. Amur S, Frueh FW, Lesko LJ, et al. Integration and use of

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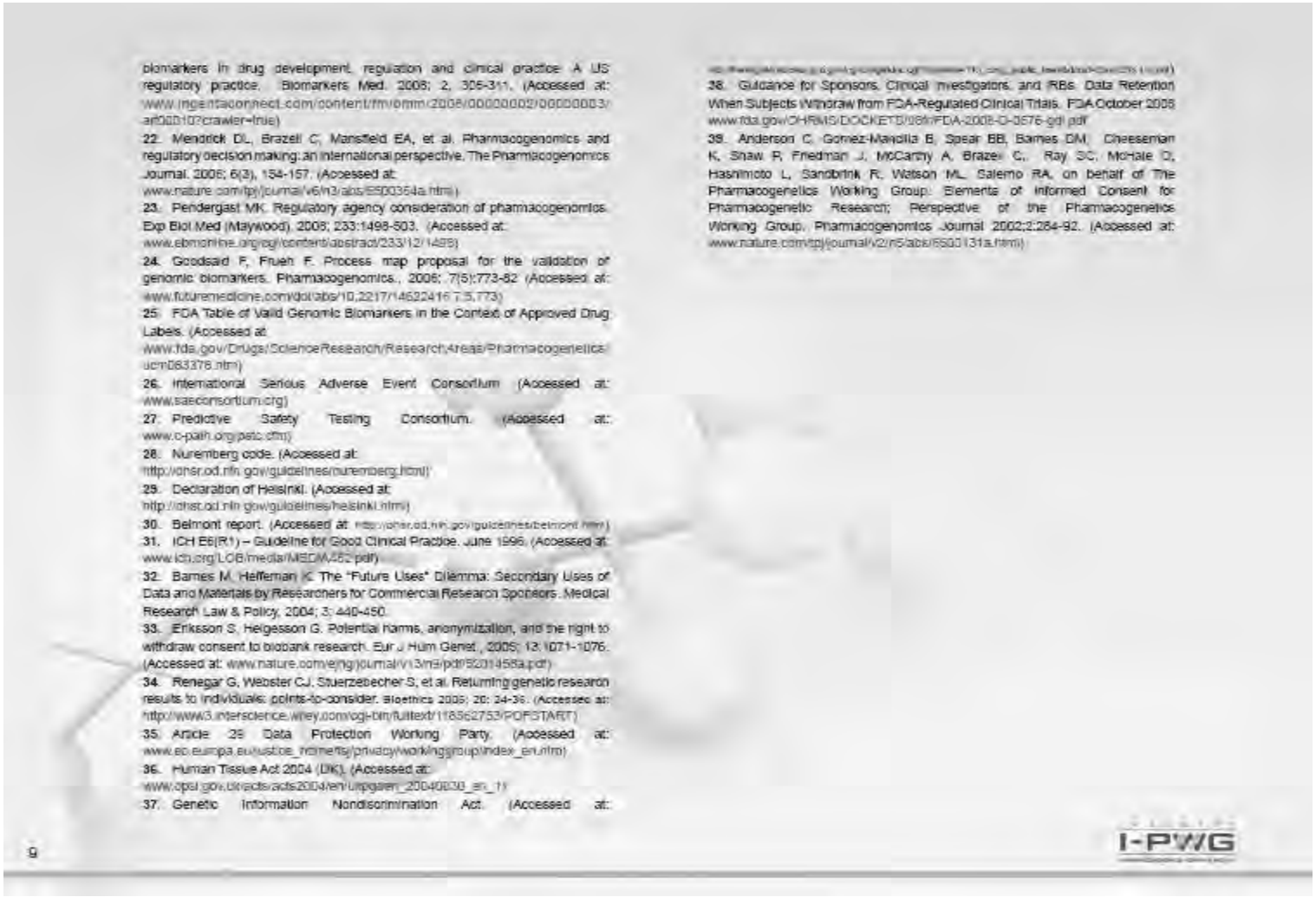

biomarkers in drug development, regulation and clinical practice: A US regulatory practice. Biomarkers Med. 2008; 2, 305-311. (Accessed at: www.ingentaconnect.com/content/fm/bmm/2008/00000002/00000003/art00010?crawler=true)
22. Mendrick DL, Brazell C, Mansfield EA, et al. Pharmacogenomics and regulatory decision making: an international perspective. The Pharmacogenomics Journal. 2006; 6(3), 154-157. (Accessed at: www.nature.com/tpj/journal/v6/n3/abs/6500364a.html)
23. Pendergast MK. Regulatory agency consideration of pharmacogenomics. Exp Biol Med (Maywood). 2008; 233:1498-503. (Accessed at: www.ebmonline.org/cgi/content/abstract/233/12/1498)
24. Goodsaid F, Frueh F. Process map proposal for the validation of genomic biomarkers. Pharmacogenomics., 2006; 7(5):773-82 (Accessed at: www.futuremedicine.com/doi/abs/10.2217/14622416.7.5.773)
25. FDA Table of Valid Genomic Biomarkers in the Context of Approved Drug Labels. (Accessed at: www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083376.htm)
26. International Serious Adverse Event Consortium (Accessed at: www.saeconsortium.org)
27. Predictive Safety Testing Consortium. (Accessed at: www.c-path.org/pstc.cfm)
28. Nuremberg code. (Accessed at: http://ohsr.od.nih.gov/guidelines/nuremberg.html)
29. Declaration of Helsinki. (Accessed at: http://ohsr.od.nih.gov/guidelines/helsinki.html)
30. Belmont report. (Accessed at: http://ohsr.od.nih.gov/guidelines/belmont.html)
31. ICH E6(R1) – Guideline for Good Clinical Practice. June 1996. (Accessed at: www.ich.org/LOB/media/MEDIA482.pdf)
32. Barnes M, Heffernan K. The "Future Uses" Dilemma: Secondary Uses of Data and Materials by Researchers for Commercial Research Sponsors. Medical Research Law & Policy, 2004; 3: 440-450.
33. Eriksson S, Helgesson G. Potential harms, anonymization, and the right to withdraw consent to biobank research. Eur J Hum Genet., 2005; 13:1071-1076. (Accessed at: www.nature.com/ejhg/journal/v13/n9/pdf/5201458a.pdf)
34. Renegar G, Webster CJ, Stuerzebecher S, et al. Returning genetic research results to individuals: points-to-consider. Bioethics 2005; 20: 34-36. (Accessed at: http://www3.interscience.wiley.com/cgi-bin/fulltext/118562753/PDFSTART)
35. Article 29 Data Protection Working Party. (Accessed at: www.ec.europa.eu/justice_home/fsj/privacy/workinggroup/index_en.htm)
36. Human Tissue Act 2004 (UK). (Accessed at: www.opsi.gov.uk/acts/acts2004/en/ukpga en_20040030_en_1)
37. Genetic Information Nondiscrimination Act. (Accessed at:
38. Guidance for Sponsors, Clinical Investigators, and IRBs. Data Retention When Subjects Withdraw from FDA-Regulated Clinical Trials. FDA October 2008 www.fda.gov/OHRMS/DOCKETS/98fr/FDA-2008-D-0576-gdl.pdf
39. Anderson C, Gomez-Mancilla B, Spear BB, Barnes DM, Cheeseman K, Shaw P, Friedman J, McCarthy A, Brazeu C., Ray SC, McHale D, Hashimoto L, Sandbrink R, Watson ML, Salerno RA, on behalf of The Pharmacogenetics Working Group. Elements of Informed Consent for Pharmacogenetic Research; Perspective of the Pharmacogenetics Working Group. Pharmacogenomics Journal 2002;2:264-92. (Accessed at: www.nature.com/tpj/journal/v2/n5/abs/6500131a.html)


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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 self-care but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Dead

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

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

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

The descriptions and grading scales found in the revised NCI-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
2L	Second-line
ADA	Anti-drug antibodies
AE	Adverse event
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
aPTT	Activated partial thromboplastin time
ASaT	All Subjects as Treated
AST	Aspartate aminotransferase
ß-hCG	Beta-human chorionic gonadotropin
BP	Blood pressure
BRAF	Proto-oncogene that encodes a protein called B-Raf
BSA	Body surface area
BSC	Best supportive care
C30	Core Questionnaire
CA 19-9	Carbohydrate antigen 19-9
CBC	Complete blood count
CD	Cluster of differentiation
CEA	Carcinoembryonic antigen
CI	Confidence interval
CO2	Carbon dioxide
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
DKA	Diabetic ketoacidosis
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
DOR	Duration of response
ECG	Electrocardiogram
ECI	Events of Clinical Interest
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic Data Capture
eDMC	External Data Monitoring Committee
EMA/EMEA	European Medicines Agency
EOC	Executive Oversight Committee
EORTC	European Organisation for Research and Treatment of Cancer
EPO	Erythropoietin
ePRO	Electronic Patient Reported Outcomes
ERC	Ethics Review Committee
EuroQoL EQ-5D	European Quality-of-Life 5 Dimension
FA	Final analysis
FBR	Future Biomedical Research
FDA	Food and Drug Administration
FFPE	Formalin-fixed paraffin-embedded
FT4	Free thyroxine
GBS	Guillain-Barre Syndrome

Abbreviation/Term	Definition
GCP	Good Clinical Practice
G-CSF	Granulocyte-colony stimulating factor
GEJ	Gastroesophageal Junction
GFR	Glomerular filtration rate
GI	Gastrointestinal
HBsAg	Hepatitis B surface antigen
HEA	Health Economic Assessment
HER2/neu	Human epidermal growth factor receptor 2
HIV	Human Immunodeficiency Virus
HPV	Human Papillomavirus
HR	Hazard ratio
HRQoL	Health-related quality-of-life
IA	Interim analysis
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IgC	Immunoglobulin constant
IgV	Immunoglobulin variable type
INR	International Normalized Ratio
irAEs	Immune-related adverse events
IRB	Institutional Review Board
irRECIST	Immune-related RECIST
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
KN	KEYNOTE
mAb	Monoclonal antibody
MMR	Mismatch repair
MSD	Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
MSI	Microsatellite instability
NA or N/A	Not applicable
NCI	National Cancer Institute
NSAID	Non-steroidal anti-inflammatory drug
NSCLC	Non-small cell lung cancer
ORR	Overall response rate
OS	Overall survival
OTC	Over-the-counter
P	Pulse
PD	Progressive disease
PD-1	Programmed cell death 1
PD-L1	Programmed cell death ligand 1
PD-L2	Programmed cell death ligand 2
PDLC	Predefined limit of change
PFS	Progression-free survival
PGt	Pharmacogenetic
PIN	Personal Identification Number
PK	Pharmacokinetic

Abbreviation/Term	Definition
PK/PD	Pharmacokinetic/pharmacodynamic
PO	Oral administration
PR	Partial response
PRO	Patient Reported Outcomes
PS	Performance Status
PT	Prothrombin Time
PTT	Partial thromboplastin time
Q2W	Every 2 weeks
Q3W	Every 3 weeks
QLQ	Quality-of-Life Questionnaire
RECIST 1.1	Response Evaluation Criteria in Solid Tumors Version 1.1
RNA	Ribonucleic acid
RR	Respiratory rate
SAE	Serious adverse events
SAP	Statistical Analysis Plan
SD	Stable disease
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SOC	System Organ Class
SOP	Standard Operating Procedures
SOTR	Solid organ transplant rejection
sSAP	Supplemental Statistical Analysis Plan
STO22	Gastric Cancer Module
T	Temperature
T1DM	Type 1 diabetes mellitus
T3	Triiodothyronine
TIL	Tumor-infiltrating lymphocytes
TSH	Thyroid-stimulating hormone
TTP	Time to progression
ULN	Upper limit of normal
US	United States
WBC	White blood cell

13.0 SIGNATURES

13.1 Sponsor's Representative

TYPED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	

13.2 Investigator

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

TYPED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	