Official Protocol Title:	A Phase II Clinical Trial of Pembrolizumab as Monotherapy and in Combination with Cisplatin+5-Fluorouracil in Subjects with Recurrent or Metastatic Gastric or Gastroesophageal Junction Adenocarcinoma (KEYNOTE-059).
NCT number:	NCT02335411
Document Date:	01-May-2020

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TITLE:

A Phase II Clinical Trial of Pembrolizumab as Monotherapy and in Combination with Cisplatin+5-Fluorouracil in Subjects with Recurrent or Metastatic Gastric or Gastroesophageal Junction Adenocarcinoma (KEYNOTE-059).

IND NUMBER: 123,482
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DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Amendment 12	01-MAY-2020	Addition of language allowing for participants to rollover to an extension study. Removal of cohort 4 from Amendment 11 which was never implemented at sites
Amendment 11/ US-specific amendment	29-MAR-2019	Addition of new cohort 4 to be treated with mFOLFOX-6, Q2W + pembrolizumab 400 mg, Q6W as first-line treatment. Amendment 11 was never implemented at sites.
Amendment 10	01-NOV-2017	Update pembrolizumab dose modification guidance upon health authority request and insertion of provision to allow more frequent survival monitoring.
Amendment 09	15-DEC-2016	Addition of requirement to discontinue treatment upon recurrent Grade 2 pneumonitis to align with the overall pembrolizumab program.
Amendment 08/ Japan-specific amendment	02-DEC-2016	Addition of requirement to discontinue treatment upon recurrent Grade 2 pneumonitis to align with the overall pembrolizumab program.

Document	Date of Issue	Overall Rationale
Amendment 07	04-NOV-2015	Update the sample size in Cohort 1 to adjust the enrollment for subjects meeting the revised eligibility criteria. PD-L1 negative subjects in Cohort 1 have passed the futility analysis. Removal of statistical hypothesis for the Cohort 1 primary efficacy objective since the objective of the study is estimation and the success of the study is determined by clinically meaningful ORR and durability of the response. Inclusion criteria updated as by the external Scientific Advisory Committee to ensure entry of subjects with the ability to participate for the full duration of the trial.
Amendment 06/ UK-specific amendment	16-JUL-2015	Addition of option for use of capecitabine instead of 5-FU (Cohort 2) in Japan only, as per health authority request. Removed the collection of the MDSC assay and QoL assessments (EORTC QLQ-C30, EORTC QLQ-ST022) from the protocol.
Amendment 05/ UK-specific amendment	30-JUN-2015	Clarify abstinence language as required by the regulatory agency in the UK.
Amendment 04	21-MAY-2015	Addition of option for use of capecitabine instead of 5-FU (Cohort 2) in Japan only, as per health authority request. Removed the collection of the MDSC assay and QoL assessments (EORTC QLQ-C30, EORTC QLQ-ST022) from the protocol.

Document	Date of Issue	Overall Rationale
Amendment 03	10-APR-2015	Removed the collection of the MDSC assay and QoL assessments (EORTC QLQ-C30, EORTC QLQ-ST022) from the protocol.
Amendment 02	16-DEC-2014	Clarifications inserted to further define what is considered safely accessible tumor for the purposes of this study.
Amendment 01	14-NOV-2014	Correction of error to wording of exclusion criteria #2 that affects the interpretation of the criterion and would impact enrollment.
Original Protocol	07-NOV-2014	Not Applicable

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 extension study language	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 are discontinued and may be enrolled in a pembrolizumab extension study	
Cover Page		Removal of US-specific amendment text	To reflect Cohort 4 removal, which was originally specific to the US
Cover Page 1.0 2.1 2.2 3.1 3.2 3.3 4.2.1 4.2.1.4	Title Trial Summary Trial Design Trial Diagram Primary Objective(s) & Hypothesis(es) Secondary Objective(s) & Hypothesis(es) Exploratory Objective(s) & Hypothesis(es) Rationale for the Trial and Selected Subject Population Cohort 4: 1L Subjects Receiving Combination Treatment with mFOLFOX 6 regimen)	Removal of Cohort 4 and associated rationales, treatment regimen, objectives, and dose modification/supportive care details.	To reflect Cohort 4 removal. Amendment 11 that included a new Cohort 4 was never implemented at sites.

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
4.2.2.2	Rationale for Pembrolizumab 400 mg Q6W dosing for Cohort 4		
4.2.3.2	Safety Endpoints		
5.2	Trial Treatments		
5.2.1.1.1	Cohort 4: Dose Selection Using a Modified Toxicity Probability Interval Design		
5.2.1.2.2	Dose Modification (Escalation/Titration/Other)		
5.2.1.2.7	Dosing Modification for Oxaliplatin		
5.2.2	Timing of Dose Administration		
5.6.2	Supportive Care Guidelines for Chemotherapy Agents		
5.7.1	Diet		
5.7.2	Contraception		
5.7.4	Use in Nursing Women		
5.8	Subject Withdrawal/Discontinuation Criteria		
6.3	Study flow chart: Initial Treatment Phase-Cohort 4 only (mFOLFOX-6)		
6.4	Second Course Phase (Retreatment)-Cohort 4 only (mFOLFOX-6)		
7.1.2.6	Pharmacokinetic/Pharmacodynamic Evaluations		
7.1.2.7.1	Baseline Tumor Imaging		
7.1.2.7.2	Tumor Imaging During Trial		
7.1.3.1	Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)		
7.1.4.1	Withdrawal/Discontinuation		
7.1.5.4.2	Follow-up Visits		
7.1.5.5	Second Course Phase (Retreatment Period)		

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
7.2.1 8.1 8.4.2 8.6.1 8.6.2 8.7 8.9 9.1 9.2	Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor Statistical Analysis Plan Summary Safety Endpoints Statistical Methods for Efficacy Analyses Statistical Methods for Safety Analyses Interim Analyses Sample size and Power Calculations Investigational Product Packaging and Labelling Information		

ADDITIONAL CHANGE(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
1.0 2.1	Trial Summary: Number of trial subjects Trial Design	Updated from 335 to 253 subjects	To reflect Cohort 4 removal
1.0	Trial Summary: Estimated duration of trial	Updated from 72 months to 36 months	To reflect Cohort 4 removal
1.0 2.1	Trial Summary: Duration of participation Trial Design	Initial treatment period: removed Cohort 4 treatment regimen	To reflect Cohort 4 removal
2.1	Trial Design	Removed Cohort 4 imaging information	To reflect Cohort 4 removal

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
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
5.1.2	Subject Inclusion Criteria	Criteria #14: Table 1 – Adequate organ Function Lab values – Creatinine row – removed oxaliplatin label information	To reflect Cohort 4 removal
5.1.3	Subject Exclusion Criteria	Removed in Criteria #12 – "oxaliplatin, leucovorin; Criteria #20 through #24 were removed	To reflect Cohort 4 removal
5.5.2	Prohibited Concomitant Medication	Removed list of concomitant medications to be used with caution associated with mFOLFOX-6 regimen	To reflect Cohort 4 removal
5.8.1	Discontinuation of Study Treatment after CR	Removed language that subjects can discontinue after 4 administrations and at least 1 treatment with pembrolizumab	To reflect Cohort 4 removal

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
5.9	Subjects Replacement Strategy	Removed language about DLT evaluation in Cohort 4	Requirements for DLT evaluation is no longer needed due to Cohort 4 removal
6.2	Second Course Phase (Retreatment with Pembrolizumab)	Footnote e: Added "See Section 7.1.2.7.3."	To clarify tumor imaging procedures during Second Course Phase
7.1.1.1.2	Consent and Collection of Specimen for Future Biomedical Research	State updated to: The investigator or qualified designee will explain the Future Biomedical Research consent to the participant, answer all of his/her questions, and obtain written informed consent before performing any procedure related to ~~the~~ Future Biomedical Research ~~sub-trial~~. A copy of the informed consent will be given to the participant.	Due to EU CTR changes that will require FBR results to be reported if FBR is indicated as a sub-study to the clinical protocol
7.1.1.8	Trial Compliance (Medication/Diet/Activity/Other)	Changed the word "witnessed" to "monitored"	To appropriately describe the work being done by the investigator and/or trial staff.

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
7.1.2.7.3 (Added)	Second Course (Retreatment) Tumor Imaging	Added Section and text describing Second Course Tumor imaging including timing and activities	To clarify tumor imaging procedures during Second Course Phase
7.1.2.7.4	Assessment of Disease	Originally Section 7.1.2.7.3 but moved to 7.1.2.7.4. Therefore, all references to Assessment of Disease was updated to 7.1.2.7.4	Due to the addition of Second Course (Retreatment) Tumor Imaging (Section 7.1.2.7.3), Assessment of Disease was moved to Section 7.1.2.7.4.
11.0	List of References	Removed 4 references that were specific to Cohort 4	To reflect Cohort 4 removal
12.2	Collection and Management of Specimens for Future Biomedical Research	Updated content under: 3. Summary of Procedures for Future Biomedical Research a. Subjects for Enrollment All subjects enrolled in the clinical trial will be considered for enrollment in ~~the~~ Future Biomedical Research ~~sub trial~~.	Due to EU CTR changes that will require FBR results to be reported if FBR is indicated as a sub-study to the clinical protocol

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 5. Biorepository Specimen Usage Any contracted third-party analyses will conform to the specific scope of analysis outlined in **future biomedical research protocol and consent** ~~this sub-trial~~. Future Biomedical Research specimens remaining with the third party after the specific analysis is performed will be reported to the sponsor.	Due to EU CTR changes that will require FBR results to be reported if FBR is indicated as a sub-study to the clinical protocol
12.8	List of Abbreviations	Removed abbreviations specific to Cohort 4	To reflect Cohort 4 removal
Throughout	Throughout	Text referencing Cohort 4 and “Cohorts 1 to 3” removed	To reflect Cohort 4 removal; protocol is no longer delineating between Cohort 4 and Cohorts 1 to 3

1.0 TRIAL SUMMARY

Abbreviated Title	A Phase II Clinical Trial of Pembrolizumab as Monotherapy and in Combination with Cisplatin+5-Fluorouracil in Subjects with Recurrent or Metastatic Gastric or Gastroesophageal Junction Adenocarcinoma (KEYNOTE-059).
Trial Phase	II
Clinical Indication	Gastric or Gastroesophageal Junction Adenocarcinoma
Trial Type	Interventional
Type of control	No Treatment Control
Route of administration	Intravenous
Trial Blinding	Unblinded Open-label
Treatment Groups	Cohort 1: Pembrolizumab 200 mg Q3W as monotherapy in 3L+ subjects Cohort 2: Pembrolizumab 200 mg Q3W in combination with cisplatin + 5-FU in 1L subjects. Sites in Japan will also administer pembrolizumab in combination with cisplatin and capecitabine as combination therapy. Cohort 3: Pembrolizumab 200 mg Q3W as monotherapy in PD-L1 positive 1L subjects
Number of trial subjects	Approximately 253 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 subject will participate in the trial from the time the subject signs the Informed Consent Form (ICF) through the final contact. After a screening period of up to 28 days, eligible subjects will be assigned by non-random assignment to one of 3 cohorts and receive treatment with pembrolizumab alone or in combination with cisplatin + 5-FU or, in Japan, cisplatin + capecitabine. Treatment Period: Duration of treatment is approximately 2 years (35 administrations of study treatment); the duration of each treatment cycle is 3 weeks. The first dose of study treatment will be on Day 1 of Cycle 1. Subjects in Cohort 2 will receive pembrolizumab 200 mg every 3 weeks (Q3W) with cisplatin + 5 FU, or, in Japan, cisplatin + capecitabine. Treatment with cisplatin will end after 6 cycles and treatment with 5-FU or, for Japan, capecitabine may continue for the duration of the treatment period. Subjects in Cohorts 1 and 3 will receive pembrolizumab 200 mg Q3W as a single agent. Treatment in all cohorts will continue until documented confirmed disease progression, unacceptable adverse event(s) (AE), intercurrent illness that prevents further administration of treatment, investigator's decision to discontinue the subject, subject withdraws consent, pregnancy of the subject, completion of approximately 2 years of treatment (35 administrations) with study medication or achievement of a complete response, or administrative reasons requiring cessation of treatment.

	Safety Follow-up: After the end of treatment, a safety follow-up visit for all subjects to monitor for adverse events will be conducted at 30 days after last dose of study treatment or before the initiation of a new anti-cancer treatment, whichever is earlier. 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 subject initiates new anticancer therapy, whichever occurs first. Follow up: Subjects who discontinue study treatment for reasons other than disease progression will have post-treatment follow-up for disease status until PD, initiating a non-study cancer treatment, withdrawing consent, or becoming lost to follow-up Second Course Phase: Subjects who discontinue study treatment with pembrolizumab monotherapy or combination treatment after 35 administrations of pembrolizumab (~2 years of treatment) for reasons other than disease progression or intolerability, or who discontinue after attaining a complete response may be eligible at the investigator's discretion for up to 1 year of retreatment with pembrolizumab only if they have experienced radiographic disease progression after stopping study treatment; this retreatment phase will be available to eligible subjects if the study remains open. Survival Follow-up: All subjects will be contacted 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 (NCT03486873) to continue protocol-defined assessments and treatment.
Randomization Ratio	N/A

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

2.0 TRIAL DESIGN

2.1 Trial Design

This is a non-randomized, multi-site, open-label trial of pembrolizumab in subjects with gastric or gastroesophageal junction adenocarcinoma. Approximately 253 subjects may be enrolled across 3 cohorts to examine the safety and efficacy of pembrolizumab as monotherapy or in combination with chemotherapy regimen:

Cohort 1: subjects who have progressed on at least 2 prior systemic treatments for advanced disease (3L+ subjects) will receive pembrolizumab as monotherapy

Cohort 2: subjects who have not previously received systemic therapy for advanced disease (1L subjects) will receive pembrolizumab in combination with cisplatin and 5-fluorouracil (5-FU). Sites in Japan will also administer pembrolizumab in combination with cisplatin and capecitabine.

Cohort 3: Programmed death-ligand 1 (PD-L1) positive subjects who have not previously received systemic therapy for advanced disease (1L subjects) will receive pembrolizumab as monotherapy.

All study subjects will continue to be evaluated every 6 to 9 weeks with radiologic imaging to assess response. Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 response rate as assessed by the central imaging vendor will be used as the primary efficacy endpoint. Standard RECIST 1.1 will be used by the investigator for treatment decisions until disease progression (PD) is determined by the investigator. The investigator will have an option of continuing study treatment until investigator determines radiographic confirmation of PD. After the initial radiographic disease progression by RECIST 1.1, clinical management of the subject will be made using an adaptation of RECIST 1.1, termed immune-related RECIST (irRECIST) to accommodate for possible tumor flare, which may be observed with immunotherapies such as pembrolizumab. Refer to Section 7.1.2.7.4.1 for details.

Adverse events will be monitored throughout the trial and graded in severity according to the guidelines outlined in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 (see Appendix 12.5).

Study treatment may continue until documented disease progression by irRECIST, unacceptable AEs, intercurrent illness that prevents further administration of treatment, investigator's decision to discontinue the subject, subject withdraws consent, pregnancy of the subject, completion of 35 administrations (~approximately 2 years) of pembrolizumab treatment, or administrative reasons requiring the cessation of treatment. Subjects who attain an investigator-confirmed complete response (CR) may consider stopping trial treatment after receiving at least 8 administrations of pembrolizumab and have received at least 2 treatments with pembrolizumab beyond the date when the initial CR was declared. Subjects who discontinue after completing 35 administrations (~2 years) of pembrolizumab treatment for reasons other than disease progression or intolerability or who discontinue after attaining a CR may be eligible for up to 1 year of retreatment after they have experienced radiographic disease progression. The decision to retreat will be at the discretion of the investigator only if no cancer treatment was administered since the last dose of pembrolizumab, the subject still meets the safety parameters listed in the Inclusion/Exclusion criteria, and the trial remains open (refer to Section 7.1.5.5 for further details).

After the end of treatment, each subject will be followed for 30 days for AE monitoring. Serious adverse events (SAEs) and Events of Clinical Interest (ECI) will be collected for 90 days after the end of treatment or 30 days after the end of treatment if the subject initiates new anticancer therapy, whichever is earlier. Subjects who discontinue treatment for reasons other than disease progression will have post-treatment follow-up for disease status until disease progression, initiating a non-study cancer treatment, withdrawing consent, or becoming lost to follow-up. All subjects will be contacted by telephone for overall survival until death, withdrawal of consent or the end of the study, whichever comes first.

The primary objectives of the trial are to determine the safety, tolerability, and objective response rate (ORR) of pembrolizumab (200 mg fixed dose Q3W) given as first and third

line monotherapy to subjects with gastric or gastroesophageal junction adenocarcinoma; to determine the safety and tolerability of pembrolizumab (200 mg Q3W) administered in combination with cisplatin and 5-FU, or cisplatin and capecitabine as first line (1L) therapy in subjects with gastric or gastroesophageal junction adenocarcinoma. Secondary objectives include progression-free survival (PFS), overall survival (OS), disease control rate (DCR), and duration of response (DOR) in all subjects and those with PD-L1 positive tumors. Exploratory objectives are planned to assess the relationship between candidate efficacy/resistance biomarkers and anti-tumor activity of pembrolizumab and clinical utility of PD-L1 assessments in newly-obtained tissue vs. archived tissue.

All subjects in all cohorts will be required to provide adequate tumor tissue for evaluation of PD-L1 expression and, based on the adequacy of the tissue sample quality for assessment of PD-L1 status, will receive notification of eligibility prior to non-random allocation. Subjects in Cohort 1 will *initially* be enrolled regardless of the PD-L1 expression status of their tumor tissue; however, after the 40th subject is enrolled, enrollment will be based on PD-L1 status. Cohort 2 will enroll without regard to the PD-L1 expression status. Subjects in Cohort 3 must express PD-L1. Additional details about the subject population are provided below in Section 2.2. Subjects receiving pembrolizumab as 1L therapy will be required to be HER2/neu negative.

If a newly-obtained tissue sample is submitted for a subject, an archived tissue sample is also requested (where available) at screening to support evaluation of the clinical utility of PD-L1 assessment in newly-obtained vs. archived tissue samples. An optional newly-obtained tissue sample (if applicable) is also requested at any time point during the study, (preference as close as possible to dosing after 9 weeks of study treatment). A biopsy is also requested at the time of discontinuation for PD but will not be required.

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.

2.2 Trial Diagram

The trial design for each cohort is depicted in schematics below.

The study will begin by enrolling subjects in Cohorts 1 and 2 concurrently. Enrollment into Cohort 3 is contingent on the availability of the PD-L1 assay. Enrollment by cohort, region/country and for the study overall will be tracked via the IXR system. Should enrollment into a particular cohort or for a region or country reach maximum capacity, subjects already in the screening period will be allowed to continue participation and will receive study treatment if eligible.

Cohort 1 subjects will receive pembrolizumab as 3L+ monotherapy (Figure 1).

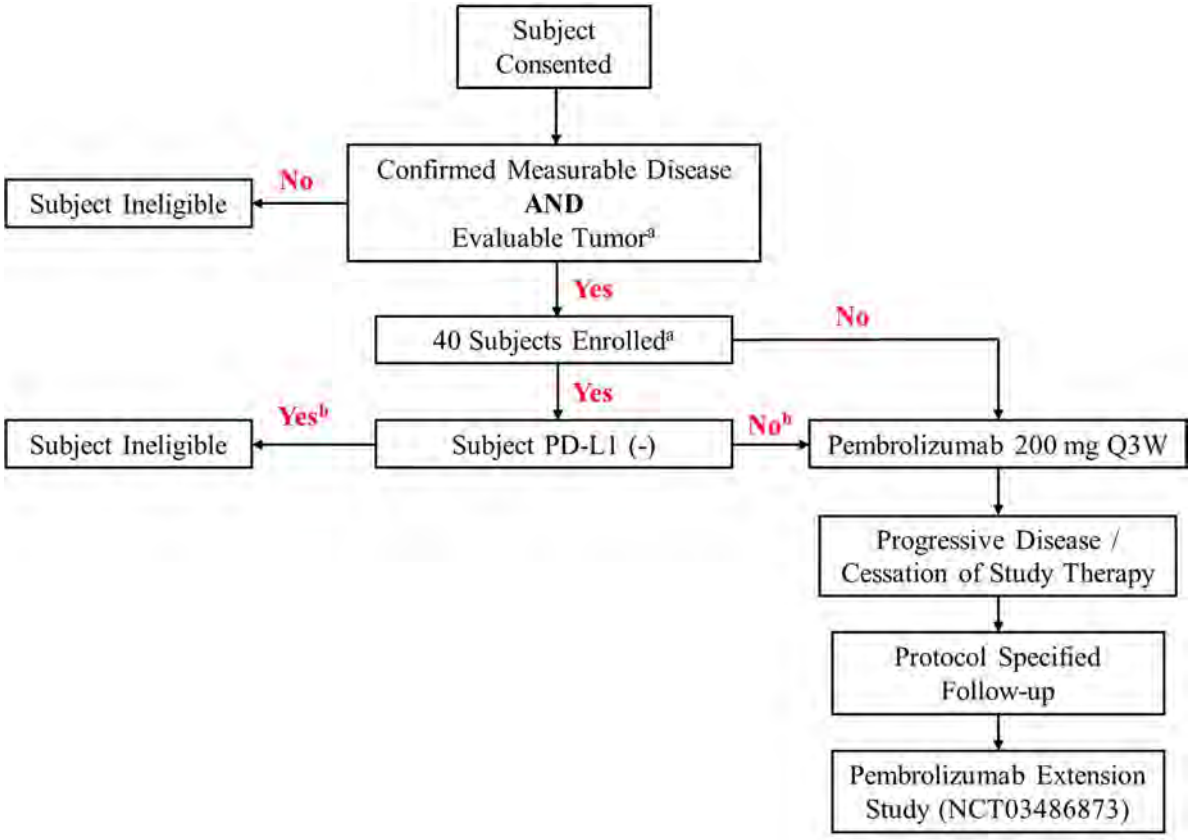

Figure 1 Cohort 1 –3L+ Monotherapy

a. Subjects may be either PD-L1 positive or negative.

b. If the response rate in PD-L1 negative subjects (from the first ~40 subjects enrolled) does not meet futility criterion, subjects that are PD-L1 negative may continue to be enrolled.

Enrollment of Cohort 1 will initially be open to all subjects regardless of PD-L1 status until the first 40 subjects are allocated to treatment (it is estimated that at this time approximately 25 PD-L1 negative subjects will be enrolled). Following enrollment of the 40th subject, enrollment will be based on PD-L1 status and PD-L1 status must be known prior to allocation to treatment. At this time, allocation of PD-L1 negative subjects to treatment will be stopped and an interim analysis will be conducted to determine if PD-L1 negative subjects show a clinically meaningful response to pembrolizumab. Allocation of PD-L1 positive subjects to treatment will continue.

As of Oct 19, 2015, an interim analysis has been performed and the external DMC has reviewed the data. The futility criterion was not met (Please see section 8.7 for the futility rule) and the DMC recommended that enrollment of PD-L1 negative subjects can be resumed. The enrollment for all subjects will stop when at least 80 all-comer (PD-L1 positive or negative) subjects meeting the revised eligibility criteria are enrolled. According to the enrollment rate projection, a total of approximately 130 subjects will be enrolled before the revised eligibility criteria are implemented. It is estimated that the overall sample size for Cohort 1 is approximately 210.

Cohort 2 subjects (1L) will receive pembrolizumab in combination with cisplatin and 5-FU. Sites in Japan will also administer pembrolizumab in combination with cisplatin and capecitabine (Figure 2).

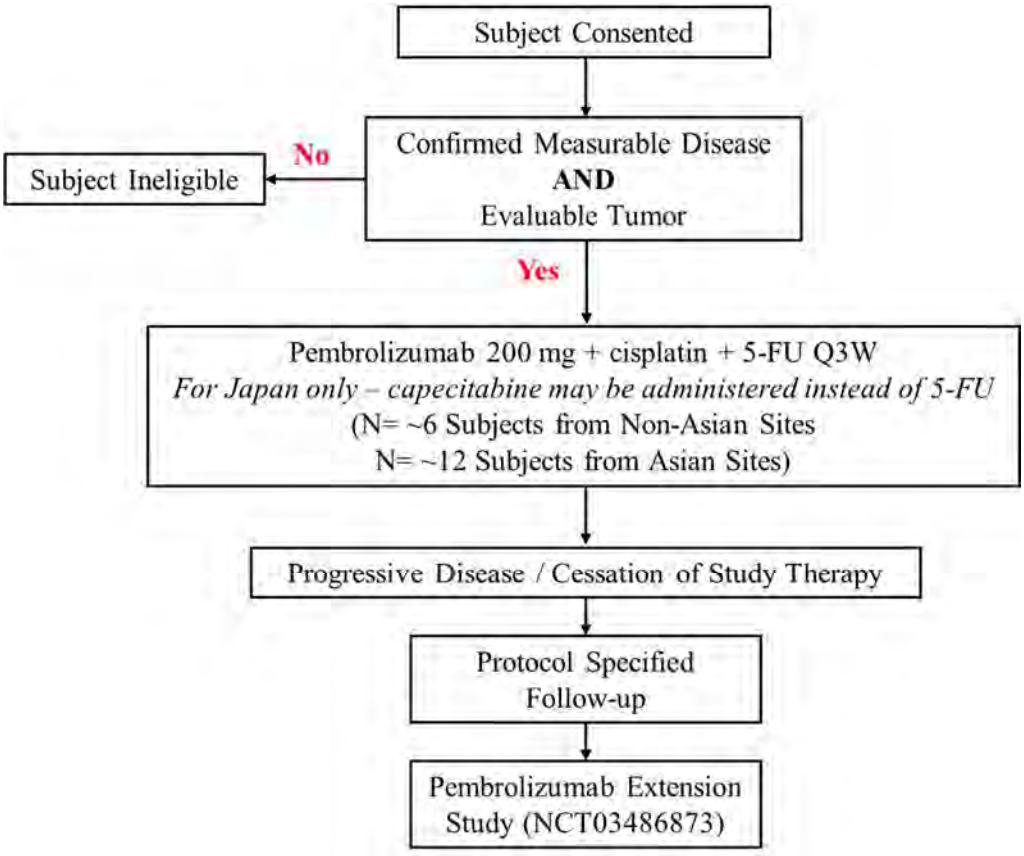

Figure 2 Cohort 2 –1L Combination Treatment

Approximately 18 subjects, regardless of PD-L1 status, will be enrolled in Cohort 2 and receive pembrolizumab as 1L therapy in combination with cisplatin+5-FU or cisplatin+capecitabine (Figure 2). A total of 6 subjects in Japan will be administered capecitabine instead of 5-FU. Approximately 12 subjects in Cohort 2 will be enrolled by sites in Asia. Approximately 6 subjects will be enrolled by sites outside of Asia. Every effort will be made to adhere to the regional or country subject allocation identified here.

Cohort 3 subjects will receive pembrolizumab as 1L monotherapy (Figure 3).

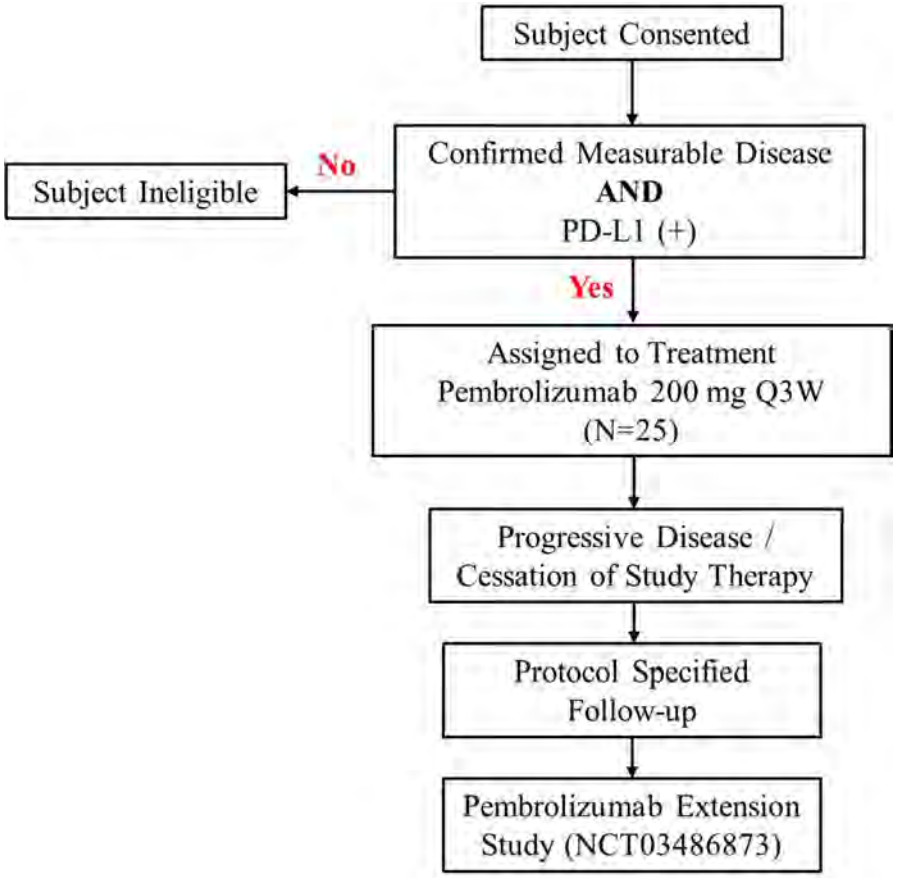

Figure 3 Cohort 3 –1L Monotherapy

Approximately 25 PD-L1 positive subjects will be enrolled in Cohort 3 and receive pembrolizumab as 1L monotherapy (Figure 3). Enrollment into Cohort 3 is contingent on the availability of the PD-L1 assay.

3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

3.1 Primary Objective(s) & Hypothesis(es)

Cohort 1: For subjects with recurrent and/or metastatic gastric or gastroesophageal adenocarcinoma who have progressed on at least 2 prior systemic treatments for advanced disease (3L+ subjects).

Cohort 2: For subjects with recurrent and/or metastatic gastric or gastroesophageal adenocarcinoma who have not previously received systemic therapy for advanced disease (1L subjects).

Cohort 3: PD-L1 positive subjects with recurrent and/or metastatic gastric or gastroesophageal adenocarcinoma who have not previously received systemic therapy for advanced disease (1L subjects).

- **Objective (within each Cohort 1, 2 and 3):** To determine the safety and tolerability of pembrolizumab administered at 200 mg Q3W dosing as monotherapy and in combination with cisplatin and 5-FU or cisplatin and capecitabine.
- **Objective (Cohort 1):** To estimate the Objective Response Rate (ORR) per RECIST 1.1 assessed by central imaging vendor in all subjects and in PD-L1 positive subjects.
- **Objective (Cohort 3):** To estimate the ORR per RECIST 1.1 assessed by central imaging vendor review.

3.2 Secondary Objective(s) & Hypothesis(es)

- **Objective (Cohort 1)**: To estimate the Duration of Response (DOR) per RECIST 1.1 by central imaging vendor in all subjects and in PD-L1 positive subjects. Supportive analyses for this objective and the primary objective include irRECIST by central imaging vendor evaluation of ORR and DOR in all subjects and in PD-L1 positive subjects as well as RECIST 1.1 and irRECIST by central imaging vendor evaluation of DCR, PFS and OS in all subjects and in PD-L1 positive subjects.
- **Objective (Cohort 2):** To estimate antitumor activity of pembrolizumab in combination with cisplatin and 5-FU or cisplatin and capecitabine for all subjects and in PD-L1 positive subjects, determined by ORR using RECIST 1.1 by central imaging vendor. Supportive analyses for this objective include irRECIST by central imaging vendor evaluation of ORR in all subjects and in PD-L1 positive subjects as well as RECIST 1.1 and irRECIST by central imaging vendor evaluation of DOR, DCR, PFS and OS in all subjects and in PD-L1 positive subjects.
- **Objective (Cohort 3):** To estimate the Duration of Response (DOR) per RECIST 1.1 by central imaging vendor in PD-L1 positive subjects. Supportive analyses for this objective and the primary objective include irRECIST by central imaging vendor evaluation of ORR and DOR in PD-L1 positive subjects as well as RECIST 1.1 and irRECIST by central imaging vendor evaluation of DCR, PFS and OS in PD-L1 positive subjects.
- **Objective (all Cohorts)**: To evaluate the relationship between PD-L1 status and efficacy endpoints in subjects receiving pembrolizumab (as monotherapy or in combination with chemotherapy) with recurrent and/or metastatic gastric or gastroesophageal junction adenocarcinoma.

3.3 Exploratory Objectives

- **Objective (all Cohorts):** To investigate the relationship between pembrolizumab treatment and biomarkers predicting response (e.g., genetic variation, serum sPDL1) utilizing newly-obtained or archival FFPE tumor tissue and/or blood (including whole blood, serum and plasma).
- **Objective (all Cohorts):** To compare performance of PD-L1 assessment in newly-obtained vs. archived tissue samples.

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

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 CD8+ T-cells and the ratio of CD8+ effector T-cells / FoxP3+ regulatory T-cells seems to correlate with improved prognosis and long-term survival in many solid tumors.

The programmed 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 CTLA-4 which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) [7, 8]. 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, 9, 10, 11]. 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 [12, 13]. 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 [14, 15]. Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells [16]. 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 [17, 18, 19, 12]. Both ligands are type I transmembrane receptors containing both IgV- and IgC-like domains in the extracellular region and contain short cytoplasmic regions with no known signaling motifs. Binding of either PD-1 ligand to PD-1 inhibits T-cell activation triggered through the T-cell receptor. PD-L1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments. PD-L2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T-cell function in peripheral tissues [12]. 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 [20]. In

gastric cancer PD-L1 and PD-L2 overexpression have recently been associated with EBV-positive tumors [21]. This suggests that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and can be an attractive target for therapeutic intervention.

Pembrolizumab 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. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an intravenous (IV) immunotherapy for advanced malignancies. Keytruda® (pembrolizumab) is indicated for the treatment of patients across a number of indications. For more details on specific indications refer to the Investigator's Brochure.

4.1.2 Pre-clinical and Clinical Trials

Therapeutic studies in mouse models have shown that administration of antibodies blocking PD-1/PD-L1 interaction enhances infiltration of tumor-specific CD8+ T-cells and leads ultimately to tumor rejection, either as a mono-therapy or in combination with other treatment modalities. Anti-mouse PD-1 or anti-mouse PD-L1 antibodies have demonstrated anti-tumor responses as a mono-therapy in models of squamous cell carcinoma, pancreatic carcinoma, melanoma and colorectal carcinoma. Blockade of the PD-1 pathway effectively promoted CD8+ T-cell infiltration into the tumor and the presence of IFN-γ, granzyme B and perforin, indicating that the mechanism of action involved local infiltration and activation of effector T-cell function in vivo [22, 23, 24, 25, 26, 27]. Experiments have confirmed the in vivo efficacy of PD-1 blockade as a mono-therapy as well as in combination with chemotherapy in syngeneic mouse tumor models (see the IB).

Clinical trials have demonstrated efficacy in multiple solid tumor indications and hematologic malignancies. Refer to pembrolizumab IB for study details.

4.1.3 Ongoing Clinical Trials

Ongoing clinical trials are being conducted in advanced melanoma, NSCLC, a number of advanced solid tumor indications and hematologic malignancies. For study details please refer to the IB.

Preliminary interim data are available from a cohort of gastric adenocarcinoma patients studied in trial KN012 [28]. KEYNOTE-012 trial is a multi-cohort Phase 1b study of which one cohort enrolled subjects with recurrent or metastatic gastric or GEJ adenocarcinoma that expressed PD-L1 (≥1% by immunohistochemistry). This cohort enrolled 39 subjects (19 from Asia and 20 outside Asia), 67% of whom had received 2 or more prior chemotherapy lines. The primary efficacy endpoint was objective response rate (ORR). Despite the heavily pre-treated patient population, Pembrolizumab monotherapy demonstrated an interim ORR of 33% by RECIST v.1.1 per investigator review (95% confidence interval [CI] 19.1%, 50.2%; all partial responses). The interim disease control rate (DCR) was 41% (95% CI 25.6%, 57.9%). ORR was similar in patients 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, patients had less

prior therapy relative to the Asian patients, and that ORR in later line patients (≥3L) was higher in the Asian group (1 PR/7 patients in the non-Asia group, 4 PR/13 patients in the Asia group). As of the data cut-off date of 14-NOV-2014, the median duration of response was 24 weeks (6 months). Based on preliminary data, there appears to be a correlation between response and degree of PD-L1 positivity.

In these gastric cancer patients in KN012, single-agent pembrolizumab at 10 mg/kg Q2W was generally well tolerated, with the type, severity, and frequency of adverse events similar to that observed in other indications (see the IB for information about adverse events in other indications). There was 1 death reported in the gastric cancer cohort. This patient had adverse events of tracheomalacia (Grade 3) and hypoxia (Grade 5). The investigator considered the Grade 5 hypoxia to be related to study treatment.

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

KEYNOTE 059 (KN059) is a Phase II, 3-cohort, single arm, open-label trial of pembrolizumab alone or in combination with 5-FU (or capecitabine) and cisplatin in subjects with advanced gastric or gastroesophageal junction adenocarcinoma (note that term gastric cancer in this protocol will refer to both gastric adenocarcinoma as well as gastroesophageal junction adenocarcinoma). It will be conducted as 3 separate cohorts: a cohort of subjects who have progressed on at least 2 prior systemic treatments for advanced disease (3L+ subjects), and 2 cohorts of subjects who have not previously received systemic therapy for advanced disease (1L subjects) - one of which consist of subjects receiving pembrolizumab in combination with different chemotherapy regimens and one will consist of subjects receiving pembrolizumab monotherapy.

The PD-L1 IHC assay planned for use in this trial will be a clinical assay with the potential to be further developed and registered. In KN012 a PD-L1 prototype IHC assay was used that is different than the assay planned for KN059. The definition of PD-L1 IHC positive in KN012 is ≥1% tumor cell staining or stromal staining. The definition of PD-L1 positive in this trial, KN059, will be generally equivalent to the definition used in KN012 [28]; the actual percent positive staining required may be different with the updated assay currently being developed for use in the trial.

4.2.1.1 Cohort 1: 3L and Later Subjects

Treatment options are limited for 3L+ gastric cancer subjects, especially in western countries, with no approved or recommended treatments. In East Asian countries, single agent chemotherapy (taxane or irinotecan) is commonly used. There is minimal data on the response to treatment in 3L or later. One study conducted at a single site in Korea reported a response rate of 3.8% in 2L or later patients receiving weekly paclitaxel [29]. Overall survival was generally similar between the 2L and 3L+, while PFS was worse in the later line (3L+) patients, with a median PFS of 1.7 months. However, these had poorer performance scores (ECOG 2-3) relative to that planned in this study. A low ORR was also observed in

the REGARD study in which 2L patients were randomized to either ramucirumab or best supportive care [30]. In contrast to the previous study, patients in REGARD had better performance scores (ECOG 0 or 1) yet the ORR was still 3% in both treatment groups. Based on the improved overall survival observed in the ramucirumab group, ramucirumab as a single agent was approved in the United States for treatment of 2L gastric cancer.

The gastric cancer proof-of-concept from KN012 data was obtained in PD-L1 positive subjects only; no data is currently available regarding the performance of pembrolizumab in PD-L1 negative subjects. Therefore, the primary efficacy hypothesis for this cohort will be in the PD-L1 positive population. However, due to the limited treatment opinions currently available, late line PD-L1 negative subjects may benefit from pembrolizumab. The performance of pembrolizumab in these subjects will be explored in approximately 25 PD-L1 negative subjects and a futility analysis will be conducted based on ORR at 9 weeks, with a futility criterion of the upper bound of the 95% confidence interval for ORR <20%. Should the efficacy of pembrolizumab be non-futile in this subgroup, then enrollment of PD-L1 negative subjects will continue and an assessment of all-comers with regard to PD-L1 will be performed at the end of the study.

This will be operationalized by enrolling up to ~40 all-comer subjects, as the PD-L1 IHC assay will not be available for subject selection at the initiation of the trial (it will be available approximately 3 months after study initiation). Assuming a 40% PD-L1 positive rate based on the data from KN012, this will give approximately 25 PD-L1 negative subjects. At this point the PD-L1 subject selection assay is expected to be available, and enrollment of PD-L1 negative subjects will stop until after the futility assessment in the subjects determined to be PD-L1 negative from these initial ~40 all-comers.

As of 19-OCT-2015, the interim analysis has been performed and the external DMC has reviewed the data. The futility criterion was not met (please see Section 8.7 for the futility rule) and the DMC recommended that enrollment of PD-L1 negative subjects can be resumed. The enrollment for all subjects will stop when at least 80 all-comer (PD-L1 positive or negative) subjects meeting the revised eligibility criteria are enrolled. According to the enrollment rate projection, a total of approximately 130 subjects will be enrolled before the revised eligibility criteria are implemented. It is estimated that the overall sample size for Cohort 1 is approximately 210.

4.2.1.2 Cohort 2: 1L Subjects Receiving Combination Treatment

Based on the results of KN012, pembrolizumab is expected to have meaningful activity in both early and late lines of therapy. Current 1L treatments for metastatic gastric cancer consist of combination chemotherapy, most often consisting of a doublet containing a platinum agent and a fluoropyrimidine agent. Western patients in good condition may receive a triple combination in which an agent from a third class (e.g., taxane or anthracycline) is added. Response rates of combination chemotherapies in these patients are generally in the 40% range. It is possible that maximal treatment benefit can be obtained by adding pembrolizumab to doublet chemotherapy in 1L subjects. Cohort 2 of this study is designed to assess the safety and tolerability of this combination regimen, with cisplatin and

5-FU as the doublet chemotherapy regimen. Sites in Japan will also administer pembrolizumab in combination with cisplatin and capecitabine as the doublet regimen. This assessment will support the use of these regimens in future global clinical trials. Based on safety and tolerability, the doses of the chemotherapies may be reduced for individual subjects or an entire cohort. This information will inform dose selection for future combination trials.

The subject population for this cohort will be all-comers with respect to the PD-L1 selection assay. It is possible that PD-L1 negative subjects could benefit from addition of pembrolizumab to chemotherapy, and the primary safety objective is not expected to be impacted by PD-L1 status. In addition, an all-comer population will necessitate a shorter enrollment time and therefore earlier availability of the key safety data to support future trials.

4.2.1.3 Cohort 3: 1L Subjects Receiving Pembrolizumab Monotherapy

The final cohort in this study will be PD-L1 positive 1L gastric cancer subjects who will receive pembrolizumab monotherapy. The objective of this cohort is to provide further data assessing the performance of pembrolizumab monotherapy in this population to support future trials of single-agent pembrolizumab in early-line patients. In KN012, the current ORR in subjects who were treatment naïve or have had one prior line of therapy, there are 3 partial responders in 9 subjects (with 3 additional subjects having stable disease). Cohort 3 of this study will provide data in an additional 25 subjects to better understand efficacy. PD-L1 positive only subjects will be enrolled in this cohort, since there are no current data in PD-L1 negative subjects and these subjects may be less likely to benefit from pembrolizumab monotherapy. Since the ORR of standard treatments for these subjects is in the range of 40%-50%, this efficacy objective is to show an ORR >35%, which would suggest that pembrolizumab may be similar to, or better than, standard of care, and support future trials with a monotherapy regimen in these subjects (e.g., pembrolizumab could have a similar ORR but long duration of response which could translate into a superior survival benefit).

4.2.2 Rationale for Dose Selection/Regimen/Modification

4.2.2.1 Rationale for Pembrolizumab 200 mg Q3W Dosing

The planned dose of pembrolizumab for Cohorts 1, 2 and 3 of this trial is 200 mg every 3 weeks (Q3W). Based on the totality of data generated in the Keytruda development program, 200 mg Q3W is the appropriate dose of pembrolizumab across all indications and regardless of tumor type. As outlined below, this dose is justified by:

- Clinical data from 8 randomized studies demonstrating flat dose- and exposure-efficacy relationships from 2 mg/kg Q3W to 10 mg/kg every 2 weeks (Q2W)
- Clinical data showing meaningful improvement in benefit-risk including overall survival at 200 mg Q3W across multiple indications

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

Among the 8 randomized dose-comparison studies, a total of 2262 subjects were enrolled with melanoma and NSCLC, covering different disease settings (treatment-naïve, previously treated, PD-L1 enriched and all-comers) and different treatment settings (monotherapy and in combination with chemotherapy). Five studies compared 2 mg/kg Q3W vs. 10 mg/kg Q3W (KN001 B2, KN001 D, KN002, KN010, and KN021), and 3 studies compared 10 mg/kg Q3W vs. 10 mg/kg Q2W (KN001 B3, KN001 F2, and KN006). All of these studies demonstrated flat dose- and exposure-response relationships across the doses studied, representing an approximate 5- to 7.5-fold difference in exposure. The 2 mg/kg (or 200 mg fixed dose) Q3W dose provided similar responses to the highest doses studied. Subsequently, flat dose- and exposure-response relationships were also observed in other tumor types, including head and neck cancer, bladder cancer, gastric cancer, and classical Hodgkin's Lymphoma, confirming 200 mg Q3W as the appropriate dose independent of the tumor type. These findings are consistent with the mechanism of action of pembrolizumab, which acts by interaction with immune cells, and not via direct binding to cancer cells.

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

Finally, population PK analysis of pembrolizumab, which characterized the influence of body weight and other subject covariates on exposure, has shown that 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 the 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.

4.2.3 Rationale for Endpoints

4.2.3.1 Efficacy Endpoints

The primary efficacy objective of this study is to evaluate the anti-tumor activity of pembrolizumab in subjects with advanced gastric cancer. Objective Response rates per RECIST 1.1 (Appendix 12.6) as assessed by the central imaging vendor will be used as the primary response rate efficacy endpoint. Objective response rate will also be used as the primary endpoint due to the single-arm design of this study.

RECIST 1.1 will be used by the local site for treatment decisions. However, RECIST 1.1 will be adapted to account for the unique tumor response profile seen with immunotherapies such as pembrolizumab. Refer to Section 7.1.2.7.4 for details.

A secondary objective of this trial is the evaluation of the relationship between PD-L1 biomarker status as assessed by immunohistochemistry and response to pembrolizumab. This objective will be evaluated using data from both the 3L+ and the 1L monotherapy cohorts. The data obtained in this trial with regard to the biomarker will inform the performance of PD-L1 assessment by IHC and may determine if the definition of PD-L1 positivity should be modified for future trials or specific populations. Fresh biopsies are currently used for PD-L1 assessment, although in this study archival biopsies will also be obtained to compare the performance of the PD-L1 IHC assay in archived versus fresh biopsies so that it may be possible to use archival biopsies in future studies.

4.2.3.2 Safety Endpoints

The primary safety objective of this trial is to characterize the safety and tolerability of pembrolizumab and pembrolizumab in combination with cisplatin + 5-FU or cisplatin + capecitabine in subjects with gastric cancer. The primary safety analysis will be based on subjects who experienced toxicities as defined by CTCAE criteria (Appendix 12.5). Safety will be assessed by quantifying the toxicities and grades experienced by subjects who have received pembrolizumab and pembrolizumab in combination with cisplatin + 5-FU or cisplatin + capecitabine , including SAEs and ECIs.

Safety will be assessed by reported adverse experiences using CTCAE, Version 4.0. The attribution to drug, time-of-onset, duration of the event, its resolution, and any concomitant medications administered will be recorded. Adverse events will be analyzed including but not limited to all AEs, SAEs, fatal AEs, and laboratory changes.

4.2.3.3 Exploratory Endpoints

4.2.3.3.1 Planned Exploratory Biomarker Research

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. This research may evaluate factors important for predicting responsiveness or resistance to pembrolizumab therapy and other immunologic targets.

Assays may include but are not be limited to:

Immunohistochemistry

PD-L1 expression in tumor tissue will be characterized by immunohistochemistry to explore the relationship between PD-L1 expression and response to treatment with pembrolizumab (this is a secondary objective of the trial). Other exploratory biomarkers (e.g., PD-1 expression, markers of T-cell phenotype) may also be evaluated.

Transcriptional Analyses

Messenger RNA (mRNA) expression profiling in archival material (biopsy specimens, peripheral blood) will be completed to assess expression of approximately 700 genes and attempt to define a gene set critical for clinical response to pembrolizumab. The hypothesis to be tested is that pembrolizumab induces responses in tumors that reflect an inflamed/ immune phenotype based on gene expression signatures capturing PD-L1 & interferon-gamma transcriptional programs. Global profiling will also be pursued. Expression of individual genes related to the immune system may also be evaluated such as immune signatures and critical cytokines (e.g., IL-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 therapy, as well as levels of PD-L1 IHC or protein in the tumor. Blood would be a less invasive component from which to measure PD-L1 protein biomarker. In addition to this specific protein biomarker, both tissue and blood derivatives can be subjected to proteomic profiling studies using a variety of platforms that could include but are not limited to immunoassay, Liquid Chromatography/Mass Spectrometry. This approach could identify novel protein biomarker that could aid in subject selection for pembrolizumab therapy.

Gene Analyses

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

In addition, understanding genetic determinants of drug response is an important 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 adverse events, the data might inform optimal use of therapies in the subject population.

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 this Future Biomedical Research sub-trial are presented in Section 12.2 - Collection and Management of Specimens for Future Biomedical Research. Additional informational material for institutional review boards/ethics committees (IRBs/ERCs) and investigational site staff is provided in Section 12.3.

4.3 Benefit/Risk

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

Additional details regarding specific benefits and risks for subjects participating in this clinical trial may be found in the accompanying 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 gastric or gastroesophageal junction 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:

For potential subjects in Cohort 1 (3L+ cohort):

1. Have received, and progressed on, at least two prior chemotherapy regimens. For the purposes of this study, perioperative, neoadjuvant, adjuvant chemotherapy regimens will not count as a prior regimen, unless the subject progressed while receiving adjuvant therapy or within 6 months of receiving adjuvant treatment. The date of progression and how progression was determined must be known with documentation available

confirming progression on or after treatment. Previous treatment regimens must have included a fluoropyrimidine and platinum doublet (as part of either a line of therapy or adjuvant treatment.

2. Be HER-2/neu negative, or, if HER2/neu positive, must have previously received treatment with trastuzumab (Note: If HER2/neu status was previously determined, that result is acceptable but documentation of status must be available; subjects with unknown status will have their HER2/neu status determined locally. Documentation of previous treatment with trastuzumab must also be provided.)

For potential subjects in Cohort 2 or 3 (1L cohorts):

3. Is HER2/neu negative.

4. Have not received prior systemic anti-cancer therapy for their metastatic or advanced gastric or gastroesophageal junction adenocarcinoma. For the purposes of this study, perioperative, neoadjuvant, adjuvant chemotherapy regimens will not count as a prior regimen, unless disease progression has occurred during or within 6 months of adjuvant chemotherapy.

For all potential subjects:

5. Be willing and able to provide written informed consent for the trial. The subject may also provide consent for Future Biomedical Research. However, the subject may participate in the main trial without participating in Future Biomedical Research.

6. Be ≥ 18 years of age on day of signing informed consent.

7. Have histologically or cytologically confirmed recurrent or metastatic gastric or gastroesophageal junction adenocarcinoma that is considered incurable by local therapies.

8. Be willing to provide newly obtained or archived tissue for PD-L1 and MSI biomarker analysis and, based on the adequacy of the tissue sample quality for assessment of PD-L1 status, have received notice of eligibility prior to non-random allocation. Newly-obtained tissue will be from the stomach and/or gastroesophageal junction (endoscopic tumor biopsy) or a metastatic location IF obtained as part of normal clinical practice. Repeat samples may be required if adequate tissue is not provided.

    a. *Note: Newly-obtained is defined as a specimen obtained up to 6 weeks (42 days) prior to initiation of treatment on Day 1 (Cycle 1) and with no additional anti-cancer treatment having been given after the specimen was obtained. Newly obtained biopsy specimens are preferred to archived; however, subjects for whom newly-obtained tissue sample cannot be submitted (e.g. inaccessible or subject safety concern), an archived specimen may be submitted. Newly-obtained (FFPE block or tissue in formalin solution) or archived specimens are preferred to slides. Refer to Section 7.1.2.8 for details.*

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

c. *Note: If emerging data demonstrates that there is no difference in the clinical utility of PD-L1 assessment in newly-obtained samples relative to archived ones, then archived samples may be acceptable in lieu of newly-obtained tissue samples. If this is the case, sites will be notified via an Administrative Memo.*

9. Be PD-L1 positive, if the subject is being allocated to a cohort which, at the time of enrollment, is only enrolling PD-L1 positive subjects.

   a. *Note: if at the time of enrollment all-comers with regard to PD-L1 status are being enrolled, then it is not necessary to know the subject's PD-L1 status prior to enrollment, but it must be confirmed that the tissue sample obtained is adequate for retrospective assessment of PD-L1 status.*

10. Have measurable disease based on RECIST 1.1 as determined by central imaging vendor. 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.*

11. Have a performance status of 0 or 1 on the ECOG Performance Scale (Appendix 12.4) within 3 days prior to the first dose of study therapy.

12. Life expectancy of at least 3 months.

13. Female subjects of childbearing potential should be willing to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 or 180 days after the last dose of study medication (Section 5.7.2). Duration of use will be determined when the subject is assigned to treatment. Subjects of childbearing potential are those who have not been surgically sterilized or have not been free from menses for > 1 year.

    Male subjects should agree to use an adequate method of contraception starting with the first dose of study therapy through 120 or 180 days after the last dose of study therapy. Duration will be determined when the subject is assigned to treatment.

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

14. Demonstrate adequate organ function as defined in Table 1. All screening labs should be performed within 3 days prior to 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 of assessment)
Renal	
Creatinine **OR** Measured or calculated creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 X upper limit of normal (ULN) **OR** ≥60 mL/min for subject with creatinine levels > 1.5 X institutional ULN Cisplatin product label should be followed for acceptable creatinine clearance rates for subjects in Cohort 2 (combination treatment) *Notes: Creatinine clearance should be calculated per institutional standard.*
Hepatic	
Total bilirubin	≤ 1.0 X ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 X ULN **OR** ≤ 5 X ULN for subjects with liver metastases
Albumin	≥3.0 g/dL
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT) Activated Partial Thromboplastin Time (aPTT)	≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants ≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants

15. Female subjects of childbearing potential should have a negative urine or serum pregnancy test within 72 hours prior to receiving the first dose of study 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. Experienced weight loss >10% over 2 months prior to first dose of study therapy.
2. Has clinical evidence of ascites by physical exam.
3. Is currently participating and receiving study therapy or has participated in a study of an investigational agent and received study therapy or used an investigational device within 4 weeks of the first dose of treatment.
4. Has active autoimmune disease that has required systemic treatment in past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.

5. 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 (prednisone 10 mg or equivalent) may be approved after consultation with the Sponsor.

6. Has had a prior anti-cancer monoclonal antibody (mAb) within 4 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to agents administered more than 4 weeks earlier.

7. 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 adverse events due to a previously administered agent.

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

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

9. Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging at least four weeks prior to the first dose of trial treatment and 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.

10. Has history of (non-infectious) pneumonitis that required steroids or has current pneumonitis.

11. Has an active infection requiring systemic therapy.

12. Has a history or current evidence of a gastrointestinal (GI) condition (e.g., inflammatory bowel disease, Crohn's disease, ulcerative colitis) or impaired liver function or diseases that in the opinion of the Investigator may significantly alter the absorption or metabolism of oral medications; any condition (e.g., known deficiency of the enzyme dihydropyrimidine dehydrogenase), therapy, or laboratory abnormality that might confound the results of the study, interfere with the participant's participation for the full duration of the study, make administration of the study drugs hazardous, or make it difficult to monitor adverse effects such that it is not in the best interest of the subject to participate (e.g., any contraindication to the use of cisplatin, 5-FU, or capecitabine for subjects in Japan, in the opinion of the treating investigator.

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

14. 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 or 180 days after the last dose of trial treatment. Duration is determined by the cohort to which the subject would be assigned.

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

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

17. Has known chronic or acute Hepatitis B (e.g., HBsAg reactive) or Hepatitis C infection (e.g., HCV RNA [qualitative] is detected).

18. 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.

19. Is or has an immediate family member (e.g., spouse, parent/legal guardian, sibling or child) who is investigational site or Sponsor staff directly involved with this trial, unless prospective IRB approval (by chair or designee) is given allowing exception to this criterion for a specific subject.

20. Has had major surgery, open biopsy, or significant traumatic injury within 28 days prior to randomization, or anticipation of the need for major surgery during the course of study intervention.

    Note: If participant has had major surgery, they must have recovered adequately from the toxicity and/or complications from the treatment prior to starting study intervention.

21. Has severe hypersensitivity (≥Grade 3) to pembrolizumab or any of the study chemotherapy agents and/or to any excipients.

22. Has a known history of active tuberculosis (TB; Bacillus tuberculosis).

23. Has had an allogeneic tissue/solid organ transplant.

5.2 Trial Treatment(s)

The treatment to be used in this trial is outlined below in Table 2.

Table 2 Trial Treatments

Drug	Dose	Dose Frequency	Route of Administration	Regimen/Treatment Period	Use
Pembrolizumab	200 mg	Q3W	IV infusion	Day 1 of each 3 week cycle	Experimental
Cisplatin	80 mg/m^2	Q3W	IV infusion	Day 1 of each 3 week cycle for 6 cycles	Combination agent
5-Fluorouracil [a] (5-FU)	800 mg/m^2	Q3W	Continuous IV infusion[b]	Day 1-5 of each 3 week cycle	Combination agent
Capecitabine (Japan only) [a]	1000 mg/m^2, BID	Q3W	Oral	Day 1-14 of each 3 week cycle	Combination agent

a. For Cohort 2, sites in Japan will administer 5-FU or capecitabine in combination with cisplatin.
b. 5-FU is continuously infused for the duration of 120 hours. Subjects enrolled prior to 059-04 should remain on the 5-FU infusion duration previously chosen for the remainder of the study.

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

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 (MK-3475) are provided in the Pharmacy Manual. Preparation and administration of the chemotherapy agents used in Cohort 2 should be completed as per the approved product label. See Sections 5.2.2.2 –5.2.2.4 for general recommendations for administration.

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 Definition of Dose Limiting Toxicity

All toxicities will be graded using NCI-CTCAE Version 4.0 based on the investigator assessment.

The occurrence of any of the following toxicities during the first 28 days of treatment will be considered a DLT, if assessed by the investigator to be related to study treatment:

- Any Grade 3 to 4 toxicity other than:
  - fatigue, or
  - nausea, vomiting, or diarrhea lasting less than 72 hours;
- Grade 3 to 4 Nausea, vomiting or diarrhea lasting 72 hours or longer despite maximal supportive care including anti-emetics, intravenous hydration, anti-diarrhea agents and short term steroid use, if indicated.
- Grade 3 to 4 thrombocytopenia or neutropenia that leads to treatment delays for >14 days.
- Grade 4 febrile neutropenia if DPD deficiency is ruled out and subject requires delay for the next cycle >14 days.
- Asymptomatic Grade 3 to 4 laboratory abnormalities will be discussed between the site investigator and sponsor before being assigned as DLT.

5.2.1.2.2 Guidelines for Dose Modification Due to Adverse Events

The Common Terminology Criteria for Adverse Events version 4.0 (CTCAE 4.0) must be used to grade the severity of adverse events.

If appropriate, the investigator may attribute each toxicity event to any of the individual chemotherapy agents used or pembrolizumab alone in the combination arms and use stepwise dose modifications according to Table 3. Pembrolizumab dose reductions are not permitted. Pembrolizumab treatment may be interrupted or discontinued due to toxicity. If a dose level reduction for toxicity occurs with any agent, the dose may not be re-escalated. Dose modifications are always based on the previous cycle.

Dose modification for cisplatin + 5-FU or capecitabine combination are detailed in Table 3. Subjects may have up to 2 dose level reductions per chemotherapy agent throughout the course of the study (Table 3). If further toxicity occurs or the criteria for resuming treatment are not met, the subject must be discontinued from chemotherapy treatment. Of note, in the event a subject in Cohort 2 is discontinued from chemotherapy treatment, the subject may still be eligible for continued treatment with pembrolizumab (DL -3 in Table 3). Refer to Table 4, Table 6, and Table 7, for dose modification guidelines for AEs related to pembrolizumab, cisplatin, 5-FU, and capecitabine (Japan only), respectively. If a subject experiences several toxicities and there are conflicting recommendations, follow the most conservative dose adjustment recommended (dose reduction appropriate to the most severe toxicity).

Reduction or with-holding of one chemotherapy agent and not the other agent is appropriate if, in the opinion of the investigator, the toxicity is clearly related to one of the study treatment. If, in the opinion of the investigator, the toxicity is related to the

combination of 2 chemotherapy agents, both treatments should be reduced (if applicable), interrupted or discontinued according to recommended dose modifications. If the toxicity is related to the combination of 3 agents, all three agents should be reduced or held according to the recommended dose modifications.

Exceptional circumstances to following the dose modification tables below may be considered after consultation with the Sponsor.

Table 3 Dose Modifications for Trial Medication

	Starting Dose	Dose Level -1	Dose Level -2	Dose Level -3
Pembrolizumab	200 mg fixed dose	Dose reductions are not permitted	Dose reductions are not permitted	Dose reductions are not permitted
Cisplatin	80 mg/m^2	60 mg/m^2	40 mg/m^2	Discontinue
5-FU	800 mg/m^2	600 mg/m^2	400 mg/m^2	Discontinue
Capecitabine (Japan Only)	1000 mg/m^2 BID	750 mg/m^2 BID	500 mg/m^2 BID	Discontinue

If a toxicity is not otherwise specified, investigators should refer to the label or local standard of care for dose adjustments. At the investigator's discretion, dose modification according to Table 3 is allowed for intolerable Grade 2-3 toxicities that are not specified in the tables below. These dose modification decisions must be documented in the subject's study records.

In Cohort 2, the number of treated subjects versus the number of subjects with a dose reduction will be monitored continuously. Appendix 12.7 provides guidance for determination of lowering the dose for the chemotherapy agents for a treatment subgroup (i.e., Asian or non-Asian) according to a mTPI method.

5.2.1.2.3 Dose Modification for Pembrolizumab

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

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

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

General instructions:

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

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

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

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

5.2.1.2.4 Dose Modification and Toxicity Management of Infusion Reactions Related to Pembrolizumab

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

Table 5 Pembrolizumab Infusion Reaction Dose Modification and Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (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 subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within one hour of stopping treatment infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. **Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.**	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab (MK-3475) with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).

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

5.2.1.2.5 Dose Modifications for Cisplatin

Please refer to criteria for cisplatin dose modification included in Table 6.

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

Category	Toxicity	Hold Cisplatin Treat-ment for Grade	Timing for Restarting Cisplatin Treatment	Dose for Restarting Cisplatin Treatment	Discontinue Cisplatin
Hematologic	Neutropenia	3[1]	Neutrophil count resolves to >1,000/mm^3	No Reduction *consider G-CSF	Toxicity does not resolve within 12 weeks of last infusion or if >-2 DL reductions exceeded
		4[1]	Neutrophil count resolves to >1,000/mm^3	Reduce by 1 DL *consider G-CSF	Toxicity does not resolve within 12 weeks of last infusion or if >-2 DL reductions exceeded
	Febrile Neutropenia	3[1]	Toxicity resolves to Grade 0-1	Reduce by 1 DL	Toxicity does not resolve within 12 weeks of last infusion or if >-2 DL reductions exceeded
		4[1]	n/a	Discontinue	Permanently discontinue Cisplatin
	Thrombocytopenia	3-4[1]	Platelet count resolves to >75,000/mm^{3}or baseline	Reduce by 1 DL	Toxicity does not resolve within 12 weeks of last infusion or if >-2 DL reductions exceeded
Non-hematologic	Creatinine Increased	2	Toxicity resolves to Grade 0-1	Reduce by 1 DL	Toxicity does not resolve within 12 weeks of last infusion or if >-2 DL reductions exceeded
		3-4[1]	Toxicity resolves to Grade 0-1	Reduce by 1 DL	Toxicity does not resolve within 12 weeks of last infusion or if >-2 DL reductions exceeded
	Ototoxicity or Sensory neuropathy	3-4[1]	Toxicity resolves to Grade 0-1	Reduce by 1 DL	Toxicity does not resolve within 12 weeks of last infusion or if >-2 DL reductions exceeded
	All other non-hematologic toxicities[2]	3-4[1]	Toxicity resolves to Grade 0-1	Reduce by 1 DL	Toxicity does not resolve within 12 weeks of last infusion or if >-2 DL reductions exceeded
	Laboratory Adverse Events	4[1]	Toxicity resolves to Grade 0-1	Reduce by 1 DL	Toxicity does not resolve within 12 weeks of last infusion or if >-2 DL reductions exceeded

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

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

5.2.1.2.6 Dose Modifications for 5-FU/Capecitabine

Please refer to criteria for 5-FU and capecitabine dose modification included in Table 7.

Table 7 Dose Modification Guidelines for 5-FU/Capecitabine Drug-Related Adverse Events

Category	Toxicity	Hold 5-FU/ capecitabine[3] Treatment for Grade	Timing for Restarting 5- FU/ capecitabine[3] Treatment	Dose for Restarting 5-FU/ capecitabine[3] Treatment	Discontinue 5-FU/ capecitabine[3]
Hematologic	Neutropenia	3[1]	Neutrophil count resolves to >1,000/mm^3	No Reduction *consider G-CSF	Toxicity does not resolve within 12 weeks of last infusion or if >-2 DL reductions exceeded
		4[1]	Neutrophil count resolves to >1,000/mm^3	Reduce by 1 DL *consider G-CSF	Toxicity does not resolve within 12 weeks of last infusion or if >-2 DL reductions exceeded
	Febrile Neutropenia	3[1]	Toxicity resolves to Grade 0-1	Reduce by 1 DL	Toxicity does not resolve within 12 weeks of last infusion or if >-2 DL reductions exceeded
		4[1]	n/a	Discontinue	Permanently discontinue 5-FU/capecitabine.
	Thrombo-cytopenia	3-4[1]	Platelet count resolves to >75,000/mm^3	Reduce by 1 DL	Toxicity does not resolve within 12 weeks of last infusion or if >-2 DL reductions exceeded
Non-hematologic	Diarrhea, Mucositis, or Hand-foot syndrome	2-3	Toxicity resolves to Grade 0-1	Reduce by 1 DL	Toxicity does not resolve within 12 weeks of last infusion or if >-2 DL reductions exceeded
		4	n/a	Discontinue	Permanently discontinue 5-FU/capecitabine.
	All other non-hematologic toxicities[2]	3-4[1]	Toxicity resolves to Grade 0-1	Reduce by 1 DL	Toxicity does not resolve within 12 weeks of last infusion or if >-2 DL reductions exceeded
	Laboratory Adverse Events	4[1]	Toxicity resolves to Grade 0-1	Reduce by 1 DL	Toxicity does not resolve within 12 weeks of last infusion or if >-2 DL reductions exceeded

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

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

3 Capecitabine applicable to sites in Japan

5.2.2 Timing of Dose Administration

All trial treatments will be administered on an outpatient basis.

For the combination portions of the study (Cohort 2), treatment will be administered in the order presented below:

Cohort 2 (pembrolizumab + cisplatin + 5-FU or capecitabine [Japan]):

Cycle 1 Day 1: Study treatment with pembrolizumab must be administered on Day 1 Cycle 1, followed by cisplatin and 5-FU or capecitabine (Japan). For administrative reasons, cisplatin followed by 5-FU may be administered up to 3 days after Day 1 Cycle 1.

Cycle 2 Onwards: Study treatment with pembrolizumab, followed by cisplatin and 5-FU or capecitabine (Japan), may be administered up to 3 days before or after the scheduled Day 1 of each cycle for administrative reasons. It is not required that pembrolizumab is given on the same day as cisplatin and 5-FU, but it must be administered before cisplatin and 5-FU or capecitabine (Japan) are administered.

Dosing interruptions are permitted in the case of medical / surgical events or logistical reasons not related to study treatment (e.g., elective surgery, unrelated medical events, subject vacation, and/or holidays). Subjects may restart study treatment as soon as clinically appropriate at the investigator discretion, and not exceeding 3 weeks from the interrupted dosing. Discussion with Sponsor should occur the investigator determines a subject cannot restart study medication within 3 weeks. The reason for interruption should be documented in the subject's study record.

5.2.2.1 Pembrolizumab

Pembrolizumab should be administered on Day 1 of each 3-week cycle after all procedures and assessments have been completed as detailed on the Trial Flow Chart (Section 6.0).

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).

5.2.2.2 Cisplatin (Cohort 2 only)

Cisplatin will be administered for up to 6 cycles of treatment. Administration of cisplatin should begin on Day 1 of each 3-week cycle following administration of pembrolizumab, as detailed in Table 2 and the Trial Flow Chart (Section 6.0). Cisplatin is given initially as a dose of 80 mg/m^2 on Day 1 of each treatment cycle using an infusion duration of 60 minutes (or according to local practice).

5.2.2.3 5-Fluorouracil (Cohort 2 only)

For Cohort 2, administration of 5-FU should begin on Day 1 of each 3-week cycle following administration of cisplatin, as detailed in Table 2 and the Trial Flow Chart (Section 6.0). 5-FU will be administered as an initial dose of 800 mg/m^2 per day as a continuous infusion for 120 hours from Day 1 to Day 5 of each treatment cycle. Subjects enrolled prior to 059-04 should remain on the 5-FU infusion duration previously chosen for the remainder of the study.

5.2.2.4 Capecitabine (Cohort 2 only)

Sites in Japan will administer pembrolizumab in combination with cisplatin and capecitabine as the doublet regimen. Administration of capecitabine should begin on Day 1 of each 3-week cycle following administration of cisplatin, as detailed in Table 2 and the Trial Flow Chart (Section 6.0). Please refer to the product label for additional guidance on administration procedures for capecitabine. Capecitabine will be administered orally as a dose of 1000 mg/m^2 twice daily from Day 1 to Day 14 of each treatment cycle.

5.2.3 Trial Blinding/Masking

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

The study team will be blinded to PD-L1 expression status (positive or negative) for all subjects participating in the initial all-comers portion of Cohort 1 until the interim analysis of Cohort 1. Following the interim analysis, the Sponsor will be unblinded to PD-L1 data. Analyses or summaries of PD-L1 biomarker status will be limited and documented after the interim analysis. See additional details regarding blinding in Section 8.2.

5.3 Randomization or Treatment Allocation

Subjects participating in this trial will be allocated by non-random assignment.

5.4 Stratification

No stratification based on age, sex or other characteristics will be used in this trial.

5.5 Concomitant Medications/Vaccinations (Allowed & Prohibited)

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

5.5.1 Acceptable Concomitant Medications

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

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 30 days after the last dose of trial treatment should be recorded for SAEs and ECIs as defined in Section 7.2.

5.5.2 Prohibited Concomitant Medication

Subjects are prohibited from receiving the following therapies during the Screening and for the duration of the study (including Second Course Phase) of this trial:

- Antineoplastic systemic chemotherapy or biological therapy not specified in this protocol
- Immunotherapy 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, varicella/zoster, yellow fever, intranasal influenza, rabies, BCG, and typhoid vaccine.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an AE of suspected immunologic etiology. The use of physiologic doses of corticosteroids (prednisone 10 mg or equivalent) may be approved after consultation with the Sponsor.

  Note 1: For the purpose of preventing chemotherapy-induced nausea/vomiting, the administration of dexamethasone should be limited to those instances when the subject is receiving high (or moderate) emetic risk chemotherapy (Cohort 2). The dose and duration of dexamethasone administration should be limited to the lowest needed to prevent and/or treat chemotherapy-related nausea and emesis.

  Note 2: Anti-emetic prophylaxis with corticosteroids per NCCN or institutional guideline is permitted.

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

Concomitant Medications to be used with caution:

- Cimetidine, metronidazole and interferons may increase levels of 5-FU.
- Subjects who are taking phenytoin in conjunction with 5-FU should be examined regularly due to a potential elevation in phenytoin plasma levels. Hepatotoxic effects (rise in alkaline phosphatase, transaminase, or bilirubin levels) are commonly observed under the treatment with 5-FU and levamisole.

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

There are no prohibited therapies during the Post-Treatment Follow-up Phase.

5.6 Rescue Medications & Supportive Care

5.6.1 Supportive Care Guidelines for Pembrolizumab

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology are detailed in Section 5.2.1.2.3, Table 4. Where appropriate, these guidelines include the use of oral or intravenous treatment with corticosteroids as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab.

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

5.6.2 Supportive Care Guidelines for Chemotherapy Agents

Pre-cisplatin treatment with corticosteroids per NCCN or institutional guidelines is permitted for subjects in Cohort 2.

Please refer to the product label or local standards of care for additional supportive measures for cisplatin, 5-FU, and capecitabine (Japan only).

5.7 Diet/Activity/Other Considerations

5.7.1 Diet

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

5.7.2 Contraception

Pembrolizumab may have adverse effects on a fetus in utero. Furthermore, it is not known if pembrolizumab has transient adverse effects on the composition of sperm. Non-pregnant, non-breast-feeding women may 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 two birth control methods can either be two barrier methods or a barrier method plus a hormonal method to prevent pregnancy.

Subjects in Cohorts 1 & 3 should start using birth control from study Visit 1 throughout the study period up to 120 days after the last dose of study treatment. Subjects in Cohort 2 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 usual lifestyle and preferred contraception for the subject.

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

5.7.3 Use in Pregnancy

If a subject inadvertently becomes pregnant while on treatment with study treatment, the subject will immediately be removed from the study. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the Sponsor without delay and within 24 hours if the outcome is a serious adverse experience (e.g., death, abortion,

congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor. If a male subject impregnates his female partner, the study personnel at the site must be informed immediately and the pregnancy reported to the Sponsor and followed as described above and in Section 7.2.2.

5.7.4 Use in Nursing Women

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

5.7.4.1 Pembrolizumab

It is unknown whether pembrolizumab is excreted in human milk.

5.7.4.2 Cisplatin

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

5.7.4.3 5-Fluorouracil

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

5.7.4.4 Capecitabine (Japan)

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

5.7.5 Photosensitivity

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

5.8 Subject Withdrawal/Discontinuation Criteria

Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the investigator or the Sponsor if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding discontinuation or withdrawal procedures; including specific details regarding withdrawal from Future Biomedical Research, are provided in Section 7.1.4 – Other Procedures.

In this trial, a subject may discontinue from treatment but continue to participate in the regularly scheduled activities, as long as the subject does not withdraw consent. For a subject who has discontinued treatment but is continuing to be monitored in the trial, he/she may be allowed to begin treatment again under certain protocol-defined circumstances if deemed medically appropriate.

A subject must be discontinued from the trial for any of the following reasons:

- The subject or legal representative (such as a parent or legal guardian) withdraws consent.

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

- The subject or legal representative (such as a parent or legal guardian) withdraws consent for treatment
- Confirmed radiographic disease progression per the terms outlined in Section 7.1.2.7.4.1
- Unacceptable adverse experiences as described in Section 5.2.1.2
- Intercurrent illness that prevents further administration of treatment
- Recurrent Grade 2 pneumonitis
- Investigator's decision to withdraw the subject
- The subject has a confirmed positive serum pregnancy test
- The subject is lost to follow-up
- Completed 35 administrations of pembrolizumab (approximately 2 years) of study treatment, whichever is later.

  Note: 35 administrations of study medication is calculated from the date of first dose. Subjects who stop study treatment after 35 administrations of pembrolizumab may be eligible for up to one year of additional pembrolizumab if they progress after stopping study treatment provided they meet the requirements detailed in Section 7.1.5.5.

- Administrative reasons

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 subject will be followed for 30 days for AE monitoring (SAE and ECI will be collected for 90 days after the end of treatment or 30 days after the end of treatment if the subject initiates new anticancer therapy, whichever is earlier, as described in Section 7.2.3.1). Subjects who discontinue for reasons other than progressive disease will have post-treatment follow-up for disease status until disease progression, initiating a non-study cancer treatment, withdrawing consent or becoming lost to follow-up. After documented disease progression each subject will be followed by telephone for overall survival until death, withdrawal of consent, or the end of the study, whichever occurs first.

5.8.1 Discontinuation of Study Treatment after CR

Discontinuation of treatment may be considered for subjects who have attained a confirmed CR that have been treated for at least 8 administrations with pembrolizumab and had at least 2 treatments with pembrolizumab) beyond the date when the initial CR was declared. Subjects who then experience radiographic disease progression may be eligible for up to one year of additional treatment with pembrolizumab via the Second Course Phase at the discretion of the investigator if no cancer treatment was administered since the last dose of pembrolizumab, the subject meets the safety parameters listed in the Inclusion/Exclusion criteria, and the trial is open. Subjects will resume pembrolizumab at the same dose and schedule at the time of initial discontinuation. Additional details are provided in Section 7.1.5.5.

5.9 Subject Replacement Strategy

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

5.10 Beginning and End of the Trial

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

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

1. Quality or quantity of data recording is inaccurate or incomplete
2. Poor adherence to protocol and regulatory requirements
3. Incidence or severity of adverse drug reaction in this or other studies indicates a potential health hazard to subjects
4. Plans to modify or discontinue the development of the study treatment

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

6.0 TRIAL FLOW CHART

6.1 Initial Treatment Phase

Trial Period:	Screening	Treatment Cycles [a] (3 weeks per cycle)						End of Treatment (last dose) or Discontinuation	Post-Treatment		
						To be repeated beyond 6 cycles					
Treatment Cycle/Title:	Visit 1	1	2	3	4	5	6		Safety Follow-up (30 days from last dose)	Follow Up Visits [b]	Survival Follow-up[r] (Phone)
Scheduling Window (Days):	-28 to -1		± 3	± 3	± 3	± 3	± 3		± 7	± 7	± 7
Informed Consent	X										
Informed Consent for FBR [c]	X										
Inclusion/Exclusion Criteria	X										
Subject Identification Card	X										
Demographics and Medical History	X										
Prior and Concomitant Medication Review	X	X	X	X	X	X	X	X	X		
Clinical Procedures/Assessments											
Review Adverse Events	X	X	X	X	X	X	X	X	X	X	
12-Lead ECG (Local)	X										
Full Physical Examination	X							X			
Directed Physical Examination		X	X	X	X	X	X				
Ht (V1 only), Wt, & Vital Signs (T/P/RR/BP)	X	X	X	X	X	X	X	X			
ECOG Performance Status	X[q]		X	X	X	X	X	X			
Trial Treatment Administration [p]		X	X	X	X	X	X				
Post-study Anticancer Therapy Status										X	Q12W
Survival Status [r]		<----------									Q12W
LOCAL Laboratory Assessments											
Pregnancy Test – Urine or Serum β-HCG [d]	X										
PT/INR and aPTT [e]	X										
Chemistry Panel [e, f]	X		X	X	X	X	X [f]	X	X		
CBC with Differential [e, g]	X		X	X	X	X	X [g]	X	X		
T3, FT4, and TSH [e, h]	X		X		X		X, then Q2 cycles		X		
Serum carcinoembryonic antigen (CEA) [e, i]	X			X		X	X	X			
Urinalysis [e]	X										
CENTRAL Laboratory Assessments											
Blood for Future Biomedical Research [c]		X									
Blood for Proteomics and Genetics [k]		X									
Blood for RNA and DNA Analysis [k]		X	X	X				X			

Trial Period:	Screening	Treatment Cycles [a] (3 weeks per cycle)						End of Treatment (last dose) or Discontinuation	Post-Treatment		
						To be repeated beyond 6 cycles			Safety Follow-up (30 days from last dose)	Follow Up Visits [b]	Survival Follow-up[r] (Phone)
Treatment Cycle/Title:	Visit 1	1	2	3	4	5	6				
Scheduling Window (Days):	-28 to -1		± 3	± 3	± 3	± 3	± 3		± 7	± 7	± 7
Efficacy Measurements											
Tumor Imaging	X [l]				X [m]		X [m]	X [n]		X [n]	
Tumor Tissue Collection [o]	X	optional biopsy (close to dosing after 9 weeks of treatment)						X optional			

a. Unless otherwise specified, assessments/procedures are to be performed prior to dose administration on Day 1 of each cycle.
b. Subjects who discontinue study treatment without documented disease progression should continue to be monitored for disease status by radiologic imaging every 6 weeks (± 7 days), and after the 1st year, every 9 weeks (±7 days) until (1) the start of new anti-cancer treatment, (2) disease progression as assessed by the central imaging vendor, (3) death, or (4) the end of the study, whichever occurs first.
c. Informed consent for the optional Future Biomedical Research (FBR) samples must be obtained before the DNA sample is collected. DNA sample for analysis should be obtained predose, on Day 1 (or with the next scheduled blood draw) as the last sample drawn or at a later date as soon as the informed consent is obtained. Detailed instructions for the collection and management of specimens for FBR are provided in the Procedures Manual and Section 12.2.
d. For women of reproductive potential, a negative pregnancy test should be performed within 72 hours prior to first dose of trial treatment. Pregnancy tests (serum and/or urine tests) should be repeated if required by local guidelines.
e. Laboratory Screening Tests should be performed within 3 days prior to first dose of treatment. For all subjects, unresolved abnormal labs resulting in drug-related AEs should be followed until resolution. Post dose lab may be collected up to 72 hours prior to the scheduled time point.
f. Chemistry will be collected on Day 1 of Cycles 2-6, then every 2 cycles. For subjects in Cohort 2 who are receiving chemotherapy, chemistry will be collected every cycle on Day 1. Japan only - for subjects receiving capecitabine, chemistry should be collected as follows for Cycles 1 and 2: Cycle 1 - Days 8 and 15 (screening chemistry labs satisfy requirement for Day 1); Cycle 2 - Days 1, 8, and 15
g. CBC w/differentials will be collected on Day 1 of Cycles 2-6, then every 2 cycles. For subjects in Cohort 2 who are receiving chemotherapy, CBC w/differentials will be collected every cycle on Day 1, 8, and 15 of Cycles 1-6 (screening CBC w/differentials labs satisfy requirement for Day 1 of Cycle 1); then on Day 1 of every cycle thereafter.
h. T3, FT4 and TSH may be analyzed by the central laboratory if cannot be done locally. FT3 may be tested locally (not via central laboratory) if T3 is not locally available
i. On treatment CEA – starting at Cycle 3, CEA will be collected every 2 cycles through Cycle 12, then every 3 cycles until end of treatment.
k. Collect prior to study treatment administration. Whole blood for Genetics/RNA and DNA analyses. Serum and plasma for Proteomics.
l. Tumor imaging at screening: Cohorts 2 & 3 - imaging will be performed within 28 days prior to the first dose of trial treatment. Cohort 1 - imaging will be performed within 14 days prior to the first dose of trial treatment; at sites where the local regulatory body and/or IRB/ERC will not permit a second tumor imaging within a 28-day period, an already available imaging scan obtained within 28 days prior to first dose may be used with the approval of the Sponsor Clinical Director. For all subjects, already available imaging scans performed as part of routine clinical management are acceptable if they are of diagnostic quality and performed within the acceptable timeframe for each cohort.
m. The first on-study tumor imaging will be performed after 9 weeks (±7 days) of study treatment, and then every 6 weeks (±7 days) thereafter (or more frequently if clinically indicated). After 1 year, imaging will be performed every 9 weeks (±7 days). Timing of imaging follows calendar days and should not be adjusted due to dose interruptions. The same imaging technique, acquisition, and processing parameters for a subject should be used throughout the trial. All scans (scheduled and unscheduled) should be submitted to the central imaging vendor as soon as possible after imaging is complete.
n. Subjects without confirmed PD who discontinue treatment will have imaging performed at the time study treatment is discontinued (i.e., date of discontinuation ± 4 week window). If a scan was obtained within 4 weeks prior to discontinuation of treatment, then imaging at treatment discontinuation is not required. Continue to monitor disease status as indicated in Section 7.1.2.7.2. Subjects who discontinue treatment after confirmed PD will not need further imaging performed during the follow-up period.
o. Tumor Tissue collection at screening may be collected up to 42 days prior to first dose of study treatment. An optional newly obtained endoscopic biopsy (if applicable) is requested during the study (preference is as close as possible to dosing after 9 weeks of treatment). An optional biopsy is also requested at the time of discontinuation for PD.
p. Refer to Section 5.2.2 regarding window for timing of dose administrations (for Day 1 Cycle 1 and Cycle 2 onwards).
q. Screening ECOG should be performed within 3 days prior to first dose of study therapy.

Trial Period:	Screening	Treatment Cycles [a] (3 weeks per cycle)						End of Treatment (last dose) or Discontinuation	Post-Treatment		
						To be repeated beyond 6 cycles					
Treatment Cycle/Title:	Visit 1	1	2	3	4	5	6		Safety Follow-up (30 days from last dose)	Follow Up Visits [b]	Survival Follow-up[r] (Phone)
Scheduling Window (Days):	-28 to -1		± 3	± 3	± 3	± 3	± 3		± 7	± 7	± 7

r. After the start of new anti-cancer treatment or documented disease progression by the central imaging vendor, whichever occurs first, the subject enters the Survival Follow-Up Phase and 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).

6.2 Second Course Phase (Retreatment)

Trial Period:	Treatment Cycles[a] (3 weeks per cycle)						End of Treatment (last dose) or Discontinuation	Post-Treatment		
					To be repeated beyond 6 cycles			Safety Follow-up (30 days from last dose)	Follow Up Visits [b]	Survival Follow-up [i] (Phone)
Treatment Cycle/Title:	1[g]	2	3	4	5	6				
Scheduling Window (Days):		± 3	± 3	± 3	± 3	± 3		± 7	± 7	± 7
Administrative Procedures										
Eligibility Criteria	X									
Concomitant Medication Review	X	X	X	X	X	X	X	X		
Clinical Procedures/Assessments										
Review Adverse Events	X	X	X	X	X	X	X	X	X	
Full Physical Examination	X						X			
Directed Physical Examination		X	X	X	X	X				
Weight and Vital Signs (T, P, RR, BP)	X	X	X	X	X	X	X	X		
ECOG Performance Status	X[h.]	X	X	X	X	X	X	X		
Pembrolizumab Administration	X	X	X	X	X	X				
Post-study Anticancer Therapy Status									X	Q12W
Survival Status [i]	<----------									Q12W
Local Laboratory Assessments										
Pregnancy Test – Urine or Serum β-HCG[c]	X									
PT/INR and aPTT	X									
Chemistry Panel[d] & CBC with Differential[d]	X[d]	X	X	X	X	X, then Q2 cycles	X	X		
T3, FT4, and TSH[d]	X		X		X, then Q2 cycles			X		
Urinalysis	X									
Efficacy Measurements										
Tumor Imaging[e]			X	X			X[f]		X[f]	

a. Unless otherwise specified, assessments/procedures are to be performed prior to dose administration on Day 1 of each cycle.
b. Subjects who discontinue study treatment without documented disease progression should continue to be monitored for disease status by radiologic imaging as indicated in Section 7.1.2.7.2.
c. For women of reproductive potential, a negative pregnancy test should be confirmed within 72 hours prior to first dose of trial retreatment. Pregnancy tests (serum and/or urine tests) should be repeated if required by local guidelines.
d. Lab test done for determining eligibility for retreatment (within 3 days prior to the first dose of trial treatment) will not need to be repeated on Day 1 of Cycle 1. After Cycle 1, lab samples can be collected up to 72 hours prior to the scheduled time point. 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.
e. Tumor imaging must be performed within 28 days prior to restarting treatment with pembrolizumab. Imaging should 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 interruptions. The same image technique, acquisition, and processing parameters should be used throughout this retreatment phase. See Section 7.1.2.7.3

Trial Period:	Treatment Cycles[a] (3 weeks per cycle)						End of Treatment (last dose) or Discontinuation	Post-Treatment		
					To be repeated beyond 6 cycles			Safety Follow-up (30 days from last dose)	Follow Up Visits [b]	Survival Follow-up [i] (Phone)
Treatment Cycle/Title:	1[g]	2	3	4	5	6				
Scheduling Window (Days):		± 3	± 3	± 3	± 3	± 3		± 7	± 7	± 7

f. Subjects without confirmed PD who discontinue study treatment should have imaging performed at the time study treatment is discontinued (i.e., date of discontinuation ±4 weeks). If a scan was obtained within 4 weeks prior to discontinuation of treatment, then imaging at treatment discontinuation is not required. Every effort should be made to continue to monitor disease status by radiologic imaging as indicated in Section 7.1.2.7.2. Subjects who discontinue treatment after confirmed PD will not need further imaging.

g. All laboratory tests for determining eligibility for retreatment are to be performed within 3 days prior to the first retreatment dose of pembrolizumab, and clinical procedures/assessments are to be performed within 3 days prior to the first retreatment dose of pembrolizumab.

h. ECOG for determining eligibility for retreatment is to be performed within 3 days prior to first dose of study therapy. ECOG for eligibility for retreatment (within 3 days prior to the first dose of trial treatment) will not need to be repeated on Day 1 of Cycle 1.

i. After the start of new anti-cancer treatment or documented disease progression by the central imaging vendor, whichever occurs first, the subject enters the Survival Follow-up Phase and 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).

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 subject's gastric or gastroesophageal junction adenocarcinoma will be recorded separately and not listed as medical history.

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

7.1.1.4.1 Disease Details

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

7.1.1.5 Prior and Concomitant Medications Review

7.1.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the subject

within 28 days before the screening visit. Prior treatment for gastric or gastroesophageal junction adenocarcinoma will be recorded separately and not listed as a prior medication.

7.1.1.5.1.1 Prior Treatment Details for Gastric or Gastroesophageal Junction Adenocarcinoma

The investigator or qualified designee will review all prior cancer treatments including systemic treatments, radiation and surgeries.

7.1.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the subject during the trial beginning at Treatment Cycle 1 through the Safety Follow-Up Visit for the Initial Treatment Phase. All medications related to reportable SAEs and ECIs should be recorded as defined in Section 7.2.

During the Second Course Phase, new medications started during the trial through the Safety Follow-Up visit should be recorded. Record all medications taken for SAEs as defined in Section 7.2.

7.1.1.5.2.1 Subsequent Anti-cancer Therapy Status

The investigator or qualified designee will review all new anti-cancer therapy initiated after the last dose of trial treatment. If a subject initiates a new anti-cancer therapy within 30 days after the last dose of trial treatment, the 30 day Safety Follow-up visit must occur before the first dose of the new therapy. Once new anti-cancer therapy has been initiated the subject will move into survival follow-up.

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 allocated, by non-random assignment, and will receive a randomization number. The randomization number identifies the subject for all procedures occurring after treatment allocation. 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.

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 while the subject is in the treatment center.

7.1.2 Clinical Procedures/Assessments

7.1.2.1 Adverse Event (AE) Monitoring

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

For subjects receiving treatment with pembrolizumab, all AEs of unknown etiology associated with pembrolizumab exposure should be evaluated to determine if the AE is of potentially immunologic etiology (termed immune-related adverse events, or irAEs).

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 physician 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 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. New clinically significant abnormal findings should be recorded as AEs.

7.1.2.3 Vital Signs

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

7.1.2.4 12-Lead Electrocardiogram

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

7.1.2.5 Eastern Cooperative Oncology Group (ECOG) Performance Status

The investigator or qualified designee will assess ECOG status (see Appendix 12.4) at screening, prior to dosing on Day 1 of each treatment cycle (except Cycle 1) and at discontinuation of trial treatment as specified in the Trial Flow Chart.

7.1.2.6 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 10, each site should stop the collection of PK and ADA samples for all subjects. Blood samples for PK and ADA collected prior to Amendment 10 will be stored and analysis will be performed if required.

7.1.2.6.1 Blood Collection for Serum Pembrolizumab (MK-3475)

Sample collection, storage and shipment instructions for serum PK samples will be provided in the Procedures Manual. PK samples should be drawn for subjects who receive pembrolizumab. Every effort should be taken to collect samples at 30 days and 3 months after end of pembrolizumab treatment.

7.1.2.6.2 Blood Collection for Anti-Pembrolizumab (MK-3475)

Sample collection, storage and shipment instructions for anti- pembrolizumab antibody samples will be provided in the Procedures Manual. Anti- pembrolizumab antibody samples should be drawn for subjects who receive pembrolizumab. Every effort should be taken to collect samples at 30 days and 3 months after end of pembrolizumab treatment for ADA. Simultaneous PK sampling is required for interpretation of ADA analysis.

7.1.2.7 Tumor Imaging and Assessment of Disease

The process for image collection and transmission to the central vendor can be found in the Site Imaging Manual. Tumor imaging may be performed by computed tomography (CT) (preferred) or magnetic resonance imaging (MRI), but **the same imaging technique, acquisition, and processing parameters should be used in a subject throughout the trial**.

All scans, scheduled and unscheduled should be submitted to the central imaging vendor as soon as possible. In determining whether or not the tumor burden has increased or decreased, investigators should consider all target lesions as well as non-target lesions.

A central imaging read based on RECIST 1.1 will be used to determine subject eligibility. The central imaging vendor will receive all images from the sites and conduct the disease assessment. The Sponsor will also receive radiologic images for a retrospective analysis of subject eligibility and treatment response to be performed by the central vendor, using RECIST 1.1. Treatment decisions will be based on the investigator's radiographic assessment of disease, and not based on central imaging vendor's assessment.

7.1.2.7.1 Baseline Tumor Imaging

To meet screening criteria, baseline tumor imaging must be performed within 14 days prior to the first dose of study treatment for potential Cohort 1 (3L+) subjects, and 28 days for potential Cohort 2, or 3 (1L) subjects. The baseline imaging scan must be submitted to the central imaging vendor for determination of measurable disease per RECIST 1.1 and inclusion into the study.

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 or 28 days prior to the first dose of study treatment, as required for the respective cohort.

For subjects enrolled in Cohort 1, a scan performed outside 14 days but within 28 days prior to the first dose of pembrolizumab may be acceptable as the baseline scan if (1) it was performed as part of routine clinical management, (2) the subject is participating at a site where the local regulatory body and/or IRB/ERC would not permit a repeat scan to be performed to meet the 14 day criteria, and (3) permission is given by the Sponsor.

7.1.2.7.2 Tumor Imaging During Trial

The first on-study imaging assessment will be performed at 9 weeks (63 days ± 7 days) after the first dose of study treatment. Subsequent imaging will be performed every 6 weeks (42 days ± 7 days), or more frequently if clinically indicated through the first year. After the first year, tumor imaging will be performed every 9 weeks. Tumor imaging will be performed every 6 weeks during the second course treatment.

Imaging should continue to be performed until whichever one of the following occurs first:

- disease progression (refer to Table 8)
- start of new anti-cancer treatment
- withdrawal of consent
- death
- end of study

Imaging should follow calendar days and not be delayed for any dose interruptions that may occur.

Timing of Repeat Imaging

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 (6 weeks later if during the first year or during second course treatment, or 9 weeks later if after the first year during the initial treatment phase), whichever is clinically indicated.

7.1.2.7.3 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.

7.1.2.7.4 Assessment of Disease – RECIST 1.1 and irRECIST

RECIST 1.1 will be applied by the central imaging vendor as the primary measure for assessment of tumor response.

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

RECIST 1.1 adapted as described below to account for the unique tumor response seen with immuno-therapeutics.

7.1.2.7.4.1 Application of irRECIST

irRECIST will be used by investigators to assess tumor response and progression after initial radiographic progression per RECIST 1.1, and make treatment decisions accordingly. In this study, there will be no confirmation from central review for irRECIST. Therefore, determination of disease status per irRECIST and subsequent decision of treatment continuation/discontinuation is per the treating physician.

If radiologic imaging verifies initial disease progression per RECIST 1.1, treatment may continue at the discretion of the investigator until repeat imaging ≥ 4 weeks later. The investigator's decision to continue treatment while awaiting repeat imaging should be based on the subject's overall clinical condition guided by the following criteria:

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

- If repeat imaging shows < 20% increase in tumor burden compared to nadir, stable or improved previous new lesion (if identified as cause for initial disease progression), and stable/improved non-target disease (if identified as cause for initial disease progression), treatment may be continued / resumed, and subsequent tumor imaging follows protocol schedule.

- If repeat imaging confirms disease progression due to any of the scenarios listed below, subjects will be discontinued from study therapy.

  - Tumor burden remains ≥20% and at least 5 mm absolute increase compared to nadir
  - Non-target disease resulting in initial disease progression is worse (qualitative)
  - New lesion resulting in initial disease progression is worse (qualitative)
  - Additional new lesion(s) since last evaluation

In determining whether or not the tumor burden has increased or decreased, investigators should consider all target lesions as well as non-target lesions.

When feasible, study treatment should not be discontinued until progression is confirmed. Subjects that are deemed clinically unstable are not required to have repeat imaging for confirmation of progressive disease. Guidance for treatment continuation/discontinuation and repeat imaging per irRECIST is described in Table 8.

Table 8 Imaging and Treatment after 1st Radiologic Evidence of PD

	Clinically Stable		Clinically Unstable	
	Imaging	Treatment	Imaging	Treatment
1st radiologic evidence of PD	Repeat imaging at ≥ 4 weeks at site to confirm PD	May continue study treatment at the investigator's discretion while awaiting confirmatory scan by site	Repeat imaging at ≥ 4 weeks to confirm PD per physician discretion only	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	Continue study treatment at the investigator's discretion	Continue regularly scheduled imaging assessments	May restart study treatment if condition has improved and/or clinically stable per investigator's discretion.
CR = complete response; PD = progressive disease; PR = partial response; SD = stable disease				

NOTE: If a subject has confirmed radiographic progression (ie, 2 scans at least 4 weeks apart demonstrating progressive disease) per irRECIST, but the subject is achieving a clinically meaningful benefit, an exception to continue treatment may be considered following consultation with the Sponsor.

7.1.2.8 Tumor Tissue Collection

Tumor tissue will be evaluated as part of screening to determine if the sample is adequate for assessment of PD-L1 status (per inclusion 8 in Section 5.1.2).

Tumor tissue sample submitted in either formalin solution or FFPE block is acceptable. If submitting unstained cut slides from FFPE block, freshly cut slides must be received by the central laboratory within 14 days from when the slides are cut.

A fine needle aspirate (FNA) or cytologic specimen will not be acceptable. Tumor tissue should be submitted in the condition described in the procedure manual.

If the subject signs the Future Biomedical Research (FBR) consent, any leftover tissue that would ordinarily be discarded at the end of the main study will be retained for FBR. Details regarding time points for collection of tumor tissue are outlined in the Trial Flow Chart – Section 6.1.

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

7.1.2.9 Blood Collections – Genetics, Proteomics and Transcriptional Analyses

Details regarding time points for blood collection to support analysis of exploratory biomarkers presented in Section 4.2.3.3.1 are outlined in the Trial Flow Chart – Section 6.1.

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

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

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

7.1.3 Laboratory Procedures/Assessments

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

7.1.3.1 Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

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

Table 9 Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Blood	Serum β-human chorionic gonadotropin (β-hCG)[a]
Hemoglobin	Alkaline phosphatase	Glucose	PT (INR)[d]
Platelet Count	Alanine aminotransferase (ALT)	Protein	aPTT[d]
WBC (total and differential) [f]	Aspartate aminotransferase (AST)	Specific gravity	Total Triiodothyronine (T3)[e]
Red Blood Cell Count	Calcium	Microscopic exam, if abnormal results are noted	Free thyroxine (free T4)
Absolute Neutrophil Count[f]	Bicarbonate/carbon dioxide[b]	Urine pregnancy test[a]	Thyroid stimulating hormone (TSH)
Absolute Lymphocyte Count[f]	Carcinoembryonic antigen (CEA)		Blood for FBR
	Chloride		Blood for Proteomics
	Creatinine		Blood for Genetics
	Glucose		Blood for Transcriptional Analysis
	Phosphorus		
	Potassium		
	Sodium		
	Total Bilirubin		
	Direct Bilirubin, if total bilirubin is elevated above ULN		
	Total protein		
	Blood Urea Nitrogen		
	Uric acid		
	Urea[c]		

a Perform on women of childbearing potential only. Urine pregnancy test is preferred. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
b. Test only if part of Standard of Care locally.
c Blood Urea Nitrogen is preferred; if not available, urea may be tested.
d Coagulation factors (PT/INR and aPTT) should be tested as part of the screening procedures for all subjects. Any subject receiving anticoagulant therapy should have coagulation factors monitored closely throughout the trial.
e Total T3 is preferred; if not available, free T3 may be tested locally. T3 and TSH may be tested centrally if testing is not available locally.
f. Absolute values or percentage per local laboratory.

Laboratory tests for screening should be performed within 3 days prior to the first dose of trial treatment. After Cycle 1, pre-dose laboratory procedures can be conducted up to 72 hours prior to dosing. Results must be reviewed by the investigator or qualified designee and found to be acceptable prior to each dose of trial treatment. For all subjects, unresolved abnormal labs resulting in drug-related AEs should be followed until resolution.

Chemistry labs will be collected on Day 1 of Cycles 2-6, then every 2 cycles for subjects in Cohort 1 and 3 (pembrolizumab monotherapy) and for subjects in Cohort 2 (Combination treatment) who are receiving only pembrolizumab (both chemotherapy agents were discontinued). For subjects in Cohort 2 who are receiving chemotherapy (with or without pembrolizumab), chemistry will be collected every cycle on Day 1.

Japan only - for subjects receiving capecitabine, chemistry should be collected as follows for Cycles 1 and 2: Cycle 1 - Days 8 and 15 (screening chemistry labs satisfy requirement for Day 1); Cycle 2 - Days 1, 8, and 15. After Cycle 2, chemistry labs will be collected every cycle on Day 1 as long as the subject is receiving treatment with either capecitabine and/or cisplatin.

CBC w/differentials will be collected on Day 1 of Cycles 2-6, then every 2 cycles for subjects in Cohort 1 and 3 (pembrolizumab monotherapy) and for subjects in Cohort 2 (Combination treatment) who are receiving only pembrolizumab (in the event both chemotherapy agents were discontinued). For subjects in Cohort 2 who are receiving chemotherapy (with or without pembrolizumab), CBC w/differentials will be collected every cycle on Day 1, 8 and 15 of Cycles 1-6 (screening CBC w/differentials labs satisfy requirement for Day 1 of Cycle 1); then on Day 1 of every cycle thereafter.

Please refer to the Trial Flow Chart (Section 6.1 and Section 6.2) for additional details regarding timing for laboratory tests.

7.1.3.2 Future Biomedical Research

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

- Blood (DNA) for future use
- Leftover tumor tissue
- Leftover blood, plasma, and serum specimens (PK/ADA, blood samples for genetics, proteomics and transcriptional (RNA and DNA) analysis)

Details for collection and management as well as the use of specimens for Future Biomedical Research can be found in Appendix 12.2 and Appendix 12.3.

7.1.4 Other Procedures

7.1.4.1 Withdrawal/Discontinuation

When a subject discontinues/withdraws from participation in the trial, all applicable activities scheduled for the end-of-treatment visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.2 - Assessing and Recording Adverse Events. Subjects who a) attain a CR or b) complete 35 administrations (approximately 2 years) of study treatment may discontinue treatment with the option of restarting treatment if they meet the criteria specified in Section 7.1.5.5. After discontinuing treatment following assessment of CR or 35 administrations of study treatment, these subjects should return to the site for a Safety Follow-up Visit (described in Section 7.1.5.4.1) and then proceed to the Follow-up Period of the study (described in Section 7.1.5.4.2).

7.1.4.1.1 Withdrawal From Future Biomedical Research

Subjects may withdraw their consent for Future Biomedical Research 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.

The study team will be blinded to PD-L1 expression status (positive or negative) for all subjects participating in the initial all-comers portion of Cohort 1 until the interim analysis of Cohort 1. Following the interim analysis, the Sponsor will be unblinded to PD-L1 data. Analyses or summaries of PD-L1 biomarker status will be limited and documented after the interim analysis. See additional details regarding blinding in Section 8.2.

7.1.4.3 Calibration of Equipment

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

7.1.5 Visit Requirements

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

7.1.5.1 Screening

Approximately 28 days prior non-random assignment to one of 3 cohorts and study treatment, potential subjects will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5.1. Screening procedures may be repeated after consultation with the Sponsor. Visit requirements are outlines in Section 6.0 – Trial Flow Chart.

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

- Laboratory tests and ECOG performance status are to be performed within 3 days prior to the first dose of trial treatment.
- For women of reproductive potential, a urine pregnancy test will be performed within 72 hours prior to the first dose of trial treatment.
- Biopsy collections may be collected up to 42 days prior to the first dose of trial treatment as presented in Sections 5.1.1 and 6.1.

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

7.1.5.2 Treatment Cycles

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

7.1.5.3 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 Safety Follow up Visit, procedures do not need to be repeated. Visit requirements are outlined in Section 6.0 – Trial Flow Chart. Specific procedure-related details are provided above in Section 7.1 – Trial Procedures. Additional details regarding subject withdrawal and discontinuation are presented in Section 5.8.

7.1.5.4 Post-Treatment

7.1.5.4.1 Safety Follow-up

The Safety Follow-Up Visit will be conducted approximately 30 days after the last dose of study treatment or before the initiation of a new anti-cancer treatment, whichever comes first.

Subjects 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

Subjects who discontinue trial treatment for a reason other than disease progression will move into the Follow-Up Phase and should be assessed every 6 weeks (42 ± 7 days) by radiologic imaging to monitor disease status. After 1 year, the imaging time point will occur every 9 weeks (± 7 days). The Sponsor may request survival status to be assessed at additional time points during the course of the study (not to exceed approximately 12 weeks). Every effort should be made to collect information regarding disease status until the start of new anti-cancer therapy, disease progression, death, end of study or if the subject begins retreatment with pembrolizumab as detailed in Section 7.1.5.5. Information regarding post-study anti-cancer treatment will be collected if new treatment is initiated.

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

7.1.5.4.3 Survival Follow-up

Once a subject experiences confirmed disease progression or starts a new anti-cancer therapy, the subject moves into the Survival Follow-Up Phase and should be contacted by telephone approximately every 12 weeks to assess for survival status until death, explicit withdrawal of consent for survival follow up, or the end of the study, whichever occurs first. Information regarding post-study anti-cancer treatment will be collected if new treatment is initiated.

7.1.5.5 Second Course Phase (Retreatment Period)

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

- **Either**
  - Stopped initial treatment with study treatment after attaining an investigator-determined confirmed CR according to RECIST 1.1, and
    - Was treated for at least 8 administrations with study treatment before discontinuing treatment.
    - Received at least 2 treatments with pembrolizumab beyond the date when the initial CR was declared.

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

AND

- Experienced an investigator-determined radiographic disease progression after stopping their initial treatment.
- Did not receive any anti-cancer treatment since the last dose of study treatment.
- Has a performance status of 0 or 1 on the ECOG Performance Scale within 3 days prior to the first dose of trial treatment.
- Demonstrates adequate organ function as detailed in Section 5.1.2. Laboratory tests are to be performed within 3 days prior to the first dose of trial treatment.
- Female subject of childbearing potential should have a negative serum or urine pregnancy test within 72 hours prior to receiving retreatment with study medication.
- Female subject of childbearing potential should be willing to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 or 180 days after the last dose of study medication (Section 5.7.2). Duration of use of contraceptives will depend on which cohort a subject is assigned. Subjects of child bearing potential are those who have not been surgically sterilized or have been free from menses for > 1 year.
- Male subject should agree to use an adequate method of contraception starting with the first dose of study treatment through 120 or 180 days after the last dose of study treatment (Section 5.7.2). Duration of use of contraceptives will depend on which cohort a subject is assigned.

- Does not have a history or current evidence of any condition, therapy, or laboratory abnormality that might interfere with the subject's participation for the full duration of the trial or is not in the best interest of the subject to participate, in the opinion of the treating investigator.

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

Visit requirements are outlined in Section 6.0 – Trial Flow Chart.

7.1.5.6 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 external Data Monitoring Committee review, interim and/or final analysis. 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 previously recorded a death event in the collection tool).

7.2 Assessing and Recording Adverse Events

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

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

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

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

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

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

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

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

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

For this trial, an overdose of:

- pembrolizumab will be defined as any dose of 1,000 mg or greater (≥5 times the indicated dose)
- any standard treatment is any dose ≥ 20% over the prescribed dose.

No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

Overdoses of cisplatin, 5-FU and capecitabine (Japan only), will be managed in accordance with the respective product label.

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

7.2.3 Immediate Reporting of Adverse Events to the Sponsor

7.2.3.1 Serious Adverse Events

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

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

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

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

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

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

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

Additionally, any serious adverse event, considered by an investigator who is a qualified physician to be related to the Sponsor's product that is brought to the attention of the investigator at any time following consent through the end of the specified safety follow-up period specified in the paragraph above, or at any time outside of the time period specified in the previous paragraph also must be reported immediately to the Sponsor.

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

7.2.3.2 Events of Clinical Interest

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

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

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

Events of clinical interest for this trial include:

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

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

ECIs (both non-serious and serious adverse events) from the date of first dose through 90 days following cessation of treatment, or 30 days after the initiation of a new anticancer therapy, whichever is earlier, need to be reported to the SPONSOR within 24 hours of the event, regardless of attribution to study treatment, consistent with standard SAE reporting guidelines and either by electronic media or paper. Sponsor Contact information can be found in the administrative binder.

Subjects should be assessed for possible ECIs prior to each dose.

7.2.3.3 Protocol-Specific Exceptions to Serious Adverse Event Reporting

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

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

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

7.2.4 Evaluating Adverse Events

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

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

Refer to Table 10 when evaluating adverse events in this study.

Table 10 Evaluating Adverse Events

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

V4.0 CTCAE Grading	**Grade 1**	**Mild; asymptomatic or mild 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 of 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 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 Data Monitoring Committee (DMC) regarding the trial.

7.3.2 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 Executive Oversight Committee 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 DMC; 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.

7.3.3 Scientific Advisory Committee

The MK3475 Gastric Cancer Program Scientific Advisory Committee (SAC) has global membership. The objective of the SAC is to engage in an end-to-end and collaborative process to obtain external scientific input on program and/or protocol design, interpretation of study results and resulting publications.

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.

8.1 Statistical Analysis Plan Summary

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

Study Design Overview	A Phase II Clinical Trial of Pembrolizumab as Monotherapy and in Combination with Cisplatin+5-Fluorouracil in Subjects with Recurrent or Metastatic Gastric or Gastroesophageal Junction Adenocarcinoma (KEYNOTE-059).
Treatment Assignment	Treatment assignment is open label.
Analysis Populations	Efficacy: All Subjects as Treated (ASaT) Safety: All Subjects as Treated (ASaT)
Primary Endpoint(s)	Cohort 2: Safety and tolerability (see Section 4.2.1.2) Cohort 1/3: Objective response rate (ORR) per RECIST 1.1 assessed by central imaging vendor
Statistical Methods for Key Efficacy Analyses	Cohort 1 (3L+ gastric cancer subjects/monotherapy): 95% CI for ORR will be calculated using Exact method based on binomial distribution. Cohort 2 (1L gastric cancer subjects/combination treatment): The primary objective is safety evaluation, and the secondary objective is the estimation of the ORR. 95% CI for ORR will be calculated using Exact method based on binomial distribution. Cohort 3 (1L gastric cancer subjects/monotherapy): 95% CI for ORR will be calculated using Exact method based on binomial distribution.
Statistical Methods for Key Safety Analyses	Count and percentage of AE will be provided.
Interim Analyses	For Cohort 1, an interim analysis will be performed for PD-L1 negative subjects in this study. Results will be reviewed by an external data monitoring committee. The interim analysis is summarized below. Details are provided in Section 8.7. • Interim Analysis 1: o Timing: To be performed when ~40 all-comer subjects have response assessment available o Testing: Futility check based on ORR assessed by central imaging vendor in PD-L1 negative subjects
Multiplicity	This is an estimation study. No multiplicity adjustment will be applied.
Sample Size	Cohort 1 (3L+ gastric cancer subjects/monotherapy): Since the futility criterion was not met, the overall sample size for Cohort 1 is approximately 210. The enrollment of Cohort 1 will stop when at least 80 all-comer subjects meeting the revised eligibility criteria are enrolled. Cohort 2 (1L gastric cancer subjects/combination treatment): There will be approximately 18 subjects enrolled. Cohort 3 (1L gastric cancer subjects/monotherapy): There will be ~25 PD-L1 positive subjects enrolled.

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.

This trial is being conducted as an open-label study. There is no randomization in the study. The Clinical Biostatistics department will generate the allocation schedule.

One planned interim analysis for Cohort 1 is described in Section 8.7. The study team will remain blinded to the PD-L1 expression level (positive or negative) for the subjects participating in the initial all-comers portion of Cohort 1 until the interim analysis of Cohort 1. Results of the interim analysis will be provided by the external unblinded statistician to the Data Monitoring Committee (DMC). The DMC will serve as the primary reviewer of the results of the interim analysis and will make recommendations in terms of whether to resume the enrollment of the PD-L1 negative subjects in Cohort 1 to the SPONSOR. Prior to study completion, the external unblinded statistician will not be involved in any discussions regarding modifications to the protocol, statistical methods, identification of protocol violators, or data validation efforts after the interim analyses. Analyses or summaries of PD-L1 biomarker status before the interim analysis will be limited and documented after the interim analysis. Following the interim analysis, the Sponsor will be unblinded to PD-L1 data.

8.3 Hypotheses/Estimation

This is an estimation study. Objectives of the study are stated in Section 3.0.

8.4 Analysis Endpoints

8.4.1 Efficacy Endpoints

Objective Response Rate (ORR): proportion of subjects in the analysis population who have complete response (CR) or partial response (PR).

Duration of Response (DOR): for subjects who demonstrate CR or PR, duration of response 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.

Disease Control Rate (DCR): for 1L subjects, DCR is defined as proportion of subjects in the analysis population who have CR or PR or stable disease (SD) for at least 6 months; for 3L+ subjects, DCR is defined as proportion of subjects in the analysis population who have CR or PR or stable disease (SD) for at least 2 months.

Progression-Free Survival (PFS): time from the date of the first dose of study medication to the first documented disease progression or death.

Overall Survival (OS): time from the date of the first dose of study medication to death due to any cause.

8.4.2 Safety Endpoints

The primary safety objective of this trial is to characterize the safety and tolerability of pembrolizumab and pembrolizumab in combination with cisplatin + 5-FU or cisplatin + capecitabine in subjects with gastric cancer. The primary safety analysis will be based on subjects who experienced toxicities as defined by CTCAE criteria. Safety will be assessed by quantifying the toxicities and grades experienced by subjects who have received pembrolizumab, including serious adverse events (SAEs) and events of clinical interest (ECIs).

Safety will be assessed by reported adverse experiences using CTCAE, Version 4.0. The attribution to study treatment, time-of-onset, duration of the event, its resolution, and any concomitant medications administered will be recorded. AEs will be analyzed including but not limited to all AEs, SAEs, fatal AEs, and laboratory changes. Consider referring to Section 4.2.3 for the initial description of safety measures.

8.5 Analysis Populations

8.5.1 Efficacy Analysis Populations

The All Subjects as Treated (ASaT) population will be used for the analysis of ORR, DCR, PFS, and OS. ASaT population consists of all subjects who received at least one dose of study treatment.

The analysis population for DOR consists of responders.

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.

At least one laboratory or vital sign measurement obtained subsequent to at least one dose of study treatment is required for inclusion in the analysis of each specific parameter. To assess change from baseline, a baseline measurement is also required.

8.6 Statistical Methods

8.6.1 Statistical Methods for Efficacy Analyses

In Cohorts 1 and 3, the primary endpoints are ORR per RECIST 1.1 assessed by central imaging vendor for all subjects and in PD-L1 positive subjects. The point estimate and 95% confidence interval will be provided using exact binomial method proposed by Clopper and Pearson (1934) [34]. Subjects in the primary analysis population (ASaT) without ORR data will be counted as non-responder.

For DOR, Kaplan-Meier (KM) curves and median estimates from the KM curves will be provided as appropriate.

Censoring rules for DOR are summarized in Table 11.

Table 11 Censoring Rules for DOR

Situation	Date of progression or censoring	Outcome
No progression nor death, no new anti-cancer therapy initiated	Last adequate assessment	Censor (non-event)
No progression nor death, new anti-cancer therapy initiated	Last adequate assessment before new anti-cancer therapy initiated	Censor (non-event)
Death or progression after ≥2 consecutive missed adequate disease assessments	Last adequate assessment prior to ≥2 missed adequate disease assessments	Censor (non-event)
Death or progression after ≤1 missed adequate disease assessments	Death or progression	End of response (Event)
Subjects are considered to have an ongoing response if censored, alive, have not progressed, have not started a new anti-cancer therapy and have not been determined to be lost to follow-up.		

For each Cohort, the efficacy endpoints, analysis population, and statistical methods (including missing data handling) that will be employed for the efficacy analyses are presented in Table 12.

Table 12 Summary of Analysis Strategy for Efficacy Endpoints

Endpoint	Statistical Method	Analysis Population	Missing data approach
Primary Endpoint			
ORR • RECIST 1.1, central imaging vendor • irRECIST, central imaging vendor	Exact method based on binomial distribution	ASaT in all below populations: Cohort 1* • all • PD-L1+ Cohort 2 • all • PD-L1+ Cohort 3 (PD-L1+ only)	Subjects with missing data are considered non-responders
Secondary Endpoints			
DCR • RECIST 1.1, central imaging vendor • irRECIST, central imaging vendor	Exact method based on binomial distribution	ASaT in all below populations: Cohort 1 • all • PD-L1+ Cohort 2 • all • PD-L1+ Cohort 3 (PD-L1+ only)	Subjects with missing data are considered as disease not under control
PFS • RECIST 1.1, central imaging vendor • irRECIST, central imaging vendor OS	Summary statistics using Kaplan-Meier method	ASaT in all below populations: Cohort 1 • all • PD-L1+ Cohort 2 • all • PD-L1+ Cohort 3 (PD-L1+ only)	Censored at last assessment date
DOR • RECIST 1.1, central imaging vendor • irRECIST, central imaging vendor	Summary statistics using Kaplan-Meier method	Responders in all below populations: Cohort 1 • all • PD-L1+ Cohort 2 • all • PD-L1+ Cohort 3 (PD-L1+ only)	Censored at last assessment date

* In Cohort 1, ORR, per RECIST 1.1 assessed by central imaging vendor for all subjects and in PD-L1+ subjects, is considered primary; all other efficacy analyses are considered supportive.
** In Cohort 2, ORR, per RECIST 1.1 assessed by central imaging vendor, for all subjects and in PD-L1+ subjects is considered secondary; all other efficacy analyses are considered supportive.

8.6.2 Statistical Methods for Safety Analyses

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

8.6.3 Summaries of Baseline Characteristics, and Demographics

The number and percentage of subjects screened, enrolled, the primary reasons for screening failure, and the primary reason for discontinuation will be displayed. Demographic variables, 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

For Cohort 1, an interim analysis will be performed for PD-L1 negative subjects. The endpoint, timing, and purpose of the interim analyses are summarized in Table 13.

The detailed process is described as below:

1. Enrollment will begin with an all-comer population. After both the PD-L1 assay is ready and ~40 all-comers enrolled, PD-L1 positive subjects will be continued enrollment, and PD-L1 negative subject enrollment will be paused.

2. An interim analysis (reviewed by external DMC) will be performed when the initially enrolled all-comers (n~40) have response assessment available. The purpose of this interim analysis is to check treatment futility on the PD-L1 negative subjects. It is estimated that approximately 25 PD-L1 negative subjects will be included in this interim analysis.

3. If the futility criterion is not met, the PD-L1 negative subject enrollment will be resumed. The trial enrollment will end when at least 80 all-comer subjects meeting the revised eligibility criteria are enrolled. If the futility criterion is met for the PD-L1 negative subjects, the trial will continue to only enroll PD-L1 positive subjects until there are at least 90 PD-L1 positive subjects.

For the PD-L1 negative subjects, the futility criterion is met if the upper bound of the 95% confidence interval of ORR is less than 20%. If the futility criterion is met then the enrollment of PD-L1 negative subjects will not be resumed.

Among the initially enrolled ~40 all-comers, the actual number of PD-L1 negative subjects could vary depending on prevalence rate. According to the futility rule defined above, if 25 PD-L1 negative subjects are included in the interim analysis, and if no responder is observed, the enrollment of PD-L1 negative subjects in Cohort 1 will not resume. Otherwise, if 1 or more responders are observed among the 25 PD-L1 negative subjects, the enrollment of the PD-L1 negative subjects will be re-opened.

Table 13 Summary of Interim Analysis Strategy

Key Endpoints for Interim Analysis	Timing of Interim Analysis	Purpose of Interim Analysis
ORR (confirmed or unconfirmed*) By RECIST 1.1, central imaging vendor assessment	Initially enrolled ~40 all-comers have response assessment available (~25 PD-L1 negative subjects provided)	Check futility for PD-L1 negative subjects
* Unconfirmed responders include those with confirmed responses and those who don't have confirmation scan yet at the cut-off date for Interim Analysis.		

As of Oct 19, 2015, an interim analysis has been performed and the external DMC has reviewed the data. The futility criterion was not met and the DMC recommended that the enrollment of PD-L1 negative subjects could be resumed.

8.8 Multiplicity

This is an estimation study. 95% confidence intervals of ORR will be provided. No multiplicity adjustment will be applied.

8.9 Sample Size and Power Calculations

Cohort 1 (3L+ gastric cancer subjects/monotherapy):

- Enrollment began with an all-comer population. By 23 July 2015, 42 all-comer subjects were enrolled and included in the interim analysis.
- Then only PD-L1 positive subjects were enrolled until the outcome of the interim analysis was determined on 19 October 2015. From 23 July 2015 to 19 October 2015, approximately 33 PD-L1 positive subjects were enrolled.
- Since the futility criterion was not met at the interim analysis, the enrollment of PD-L1 negative subjects will resume. Enrollment after the interim analysis will not stop until at least 80 all-comer subjects meeting the revised eligibility criteria are enrolled. Since the implementation of the amendment takes time, it is estimated that approximately 135 all-comer subjects will be enrolled after the interim analysis, including about 55 all-comer subjects enrolled under the original protocol and 80 under the amendment.

Thus, it is estimated that the overall sample size for Cohort 1 is approximately 210.

Table 14 shows the two-sided 95% CI of ORR with 210 subjects for different observed response rates. With 210 subjects, if there are at least 31 responders observed, the lower bound of the 95% confidence interval for ORR will be above 10%.

Table 14 Two-sided 95% CI of ORR with 210 Subjects

Number of observed responders	ORR estimates	95% CI of ORR (%)
30	14.3%	(9.9, 19.8)
31	14.8%	(10.3, 20.3)
32	15.2%	(10.7, 20.8)
33	15.7%	(11.1, 21.4)

Assuming the prevalence of PD-L1 positive is 50% based on the interim analysis and ~33 PD-L1 positive subjects are enrolled during the period of enrolling only PD-L1 positive subjects; there will be a total of approximately 120 PD-L1 positive subjects in Cohort 1. Table 15 shows the two-sided 95% CI of ORR with 120 PD-L1 positive subjects for different response rates.

Table 15 Two-sided 95% CI of ORR with 120 PD-L1 Positive Subjects

Number of observed responders	ORR estimates	95% CI of ORR (%)
19	15.8%	(9.8, 23.6)
20	16.7%	(10.5, 24.6)
21	17.5%	(11.2, 25.5)
22	18.3%	(11.9, 26.4)

Table 16 shows the two-sided 95% CI of ORR with 80 all-comer subjects meeting the revised eligibility criteria for different observed response rates.

Table 16 Two-sided 95% CI of ORR with 80 Subjects Meeting Revised Eligibility Criteria

Number of observed responders	ORR estimates	95% CI of ORR (%)
14	17.5%	(9.9, 27.6)
15	18.8%	(10.9, 29.0)
16	20.0%	(11.9, 30.4)
17	21.3%	(12.9, 31.8)

Cohort 2 (1L gastric cancer subjects/combination treatment): There will be approximately 18 subjects enrolled for all-comer population. Table 17 shows the two-sided 95% CI of AE rate with 18 subjects.

Table 17 Two-sided 95% CI of AE incidence rate with 18 Subjects

Number of AE	AE incidence rate estimates	95% CI of incidence rate (%)
2	11.1%	(1.4, 34.7)
4	22.2%	(6.4, 47.6)
5	27.7%	(9.7, 53.5)
7	38.9%	(17.3, 64.2)
9	50.0%	(26.0, 73.9)

Cohort 3 (1L gastric cancer subjects/monotherapy): There will be ~25 PD-L1 positive subjects enrolled in Cohort 3. Using Bayesian sample size methods and assuming a uniform prior for the response rate (beta-binomial prior with beta (1, 1)), if we observe no more than 8 responders (i.e. observed ORR ≤32%), there is ≥77% posterior probability that the true ORR is less than 40% (ORR from Standard of Care).

8.10 Subgroup Analyses and Effect of Baseline Factors

Efficacy analyses will be performed within the following subgroups:

- Subjects classified based on PD-L1 biomarker status as appropriate;
- Subjects in Cohort 1 meeting the revised eligibility criteria.

8.11 Compliance (Medication Adherence)

Study drug accountability data for MK-3475 will be collected during the study. Any deviation from protocol-directed administration will be reported.

8.12 Extent of Exposure

Extent of Exposure for a subject is defined as number of cycles in which the subject receives the study medication infusion. Summary statistics will be provided on Extent of Exposure for ASaT population.

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 18.

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 18 Product Descriptions

Product Name & Potency	Dosage Form	Additional Information
MK-3475 25 mg/mL, 4 mL	Injection	Provided centrally by the Sponsor
Cisplatin 1 mg/mL, 50 mL	Injection	Provided centrally by the Sponsor or locally by the trial site, subsidiary or designee
5-Fluorouracil 50 mg/mL, 20 mL	Injection	Provided centrally by the Sponsor or locally by the trial site, subsidiary or designee

All supplies indicated in Table 18 will be provided per the Additional Information field depending on local country operational or regulatory requirements.

Any commercially available product not included in Table 18 will be provided by the trial site, subsidiary or designee. Every attempt should be made to source these supplies from a single lot/batch number.

The trial site is responsible to record the lot number, manufacturer and expiry date for any locally purchased product as per local guidelines unless otherwise instructed by the Sponsor.

9.2 Packaging and Labeling Information

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

Subjects will receive open label vials and/or kits for every 3-week dosing.

9.3 Clinical Supplies Disclosure

This trial is open-label; therefore, the subject, the trial site personnel, the Sponsor and/or designee are not blinded. Treatment (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 Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the Sponsor of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to the Clinical Trials Data Bank, http://www.clinicaltrials.gov. 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 FDAMA/FDAAA 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 FDAMA/FDAAA are that of the Sponsor and agrees not to submit any information about this trial or its results to the Clinical Trials Data Bank.

10.5 Quality Management System

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

10.6 Data Management

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

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

10.7 Publications

This trial is intended for publication, even if terminated prematurely. Publication may include any or all of the following: posting of a synopsis online, abstract and/or presentation at a scientific conference, or publication of a full manuscript. The Sponsor will work with the authors to submit a manuscript describing trial results within 12 months after the last data become available, which may take up to several months after the last subject visit in some cases such as vaccine trials. However, manuscript submission timelines may be extended on

OTC trials. For trials intended for pediatric-related regulatory filings, the investigator agrees to delay publication of the trial results until the Sponsor notifies the investigator that all relevant regulatory authority decisions on the trial drug have been made with regard to pediatric-related regulatory filings. Merck will post a synopsis of trial results for approved products on www.clinicaltrials.gov by 12 months after the last subject's last visit for the primary outcome, 12 months after the decision to discontinue development, or product marketing (dispensed, administered, delivered or promoted), whichever is later.

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

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

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

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

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12.0 APPENDICES

12.1 Merck Code of Conduct for Clinical Trials

Merck*
Code of Conduct for Clinical Trials

I. Introduction

A. Purpose

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

B. Scope

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

II. Scientific Issues

A. Trial Conduct

1. Trial Design

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

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

2. Site Selection

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

3. Site Monitoring/Scientific Integrity

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

B. Publication and Authorship

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

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

III. Subject Protection

A. IRB/ERC review

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

B. Safety

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

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

C. Confidentiality

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

D. Genomic Research

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

IV. Financial Considerations

A. Payments to Investigators

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

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

B. Clinical Research Funding

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

C. Funding for Travel and Other Requests

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

V. Investigator Commitment

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

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

12.2 Collection and Management of Specimens for Future Biomedical Research

1. Definitions

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

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

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

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research

The specimens collected in this trial as outlined in Section 7.1.3.2 – 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 subject is having blood drawn for other trial purposes. Specimens like tissue and bone marrow will usually be obtained at a time when the subject is having such a procedure for clinical purposes.

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

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

4. Confidential Subject Information for Future Biomedical Research

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

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

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

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

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

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

5. Biorepository Specimen Usage

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

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

Future Biomedical Research specimens remaining with the third party after the specific analysis is performed will be reported to the Sponsor.

6. Withdrawal From Future Biomedical Research

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

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

7. Retention of Specimens

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

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

8. Data Security

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

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

9. Reporting of Future Biomedical Research Data to Subjects

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

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

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

10. Gender, Ethnicity and Minorities

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

11. Risks Versus Benefits of Future Biomedical Research

For future biomedical research, risks to the subject have been minimized. Risks include those associated with venipuncture to obtain the whole blood specimen. This specimen will be obtained at the time of routine blood specimens drawn in the main trial.

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

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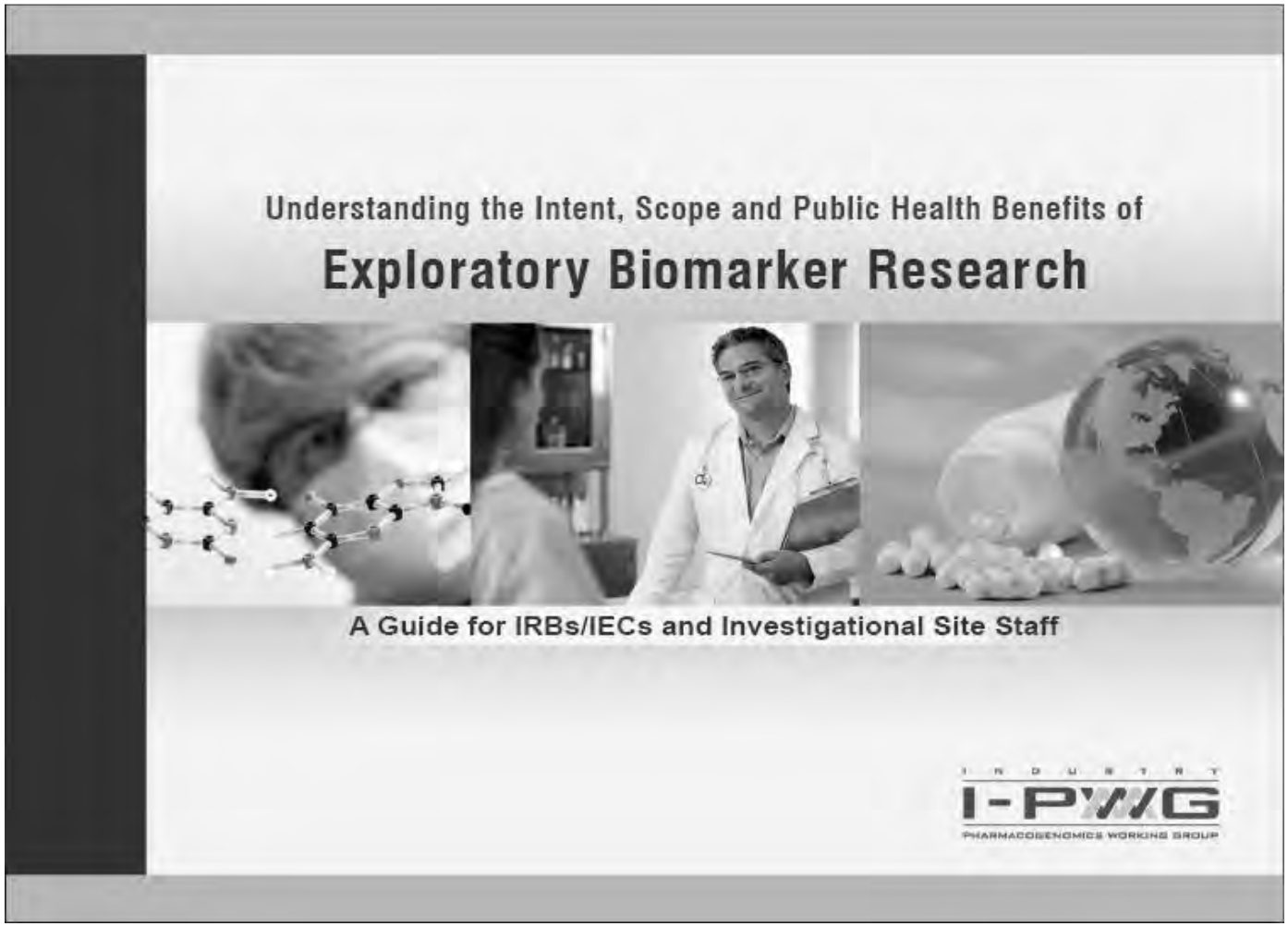
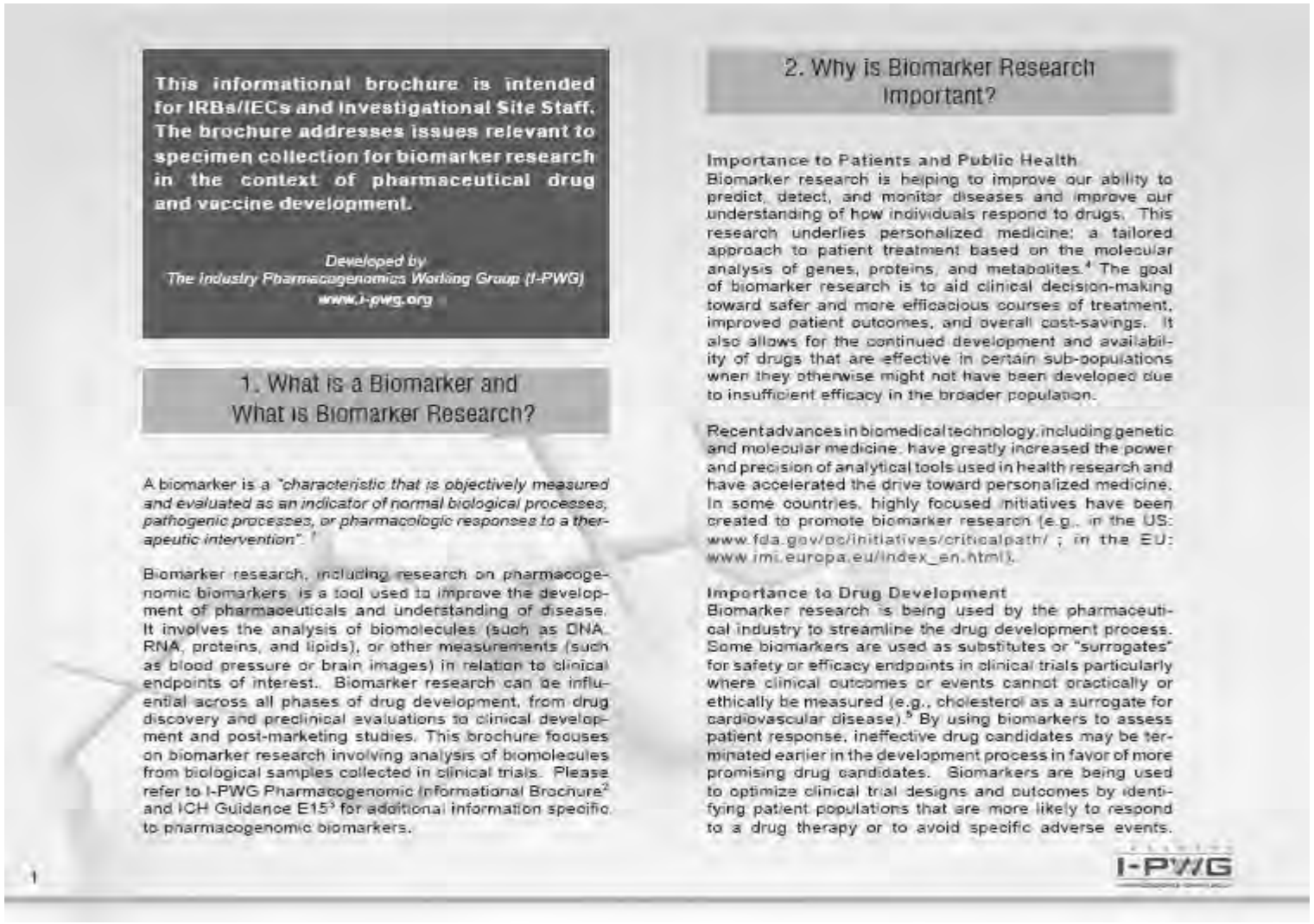
12.3 Understanding the Intent, Scope and Public Health Benefits of Exploratory Biomarker Research: A Guide for IRBs/IECs and Investigational Site Staff





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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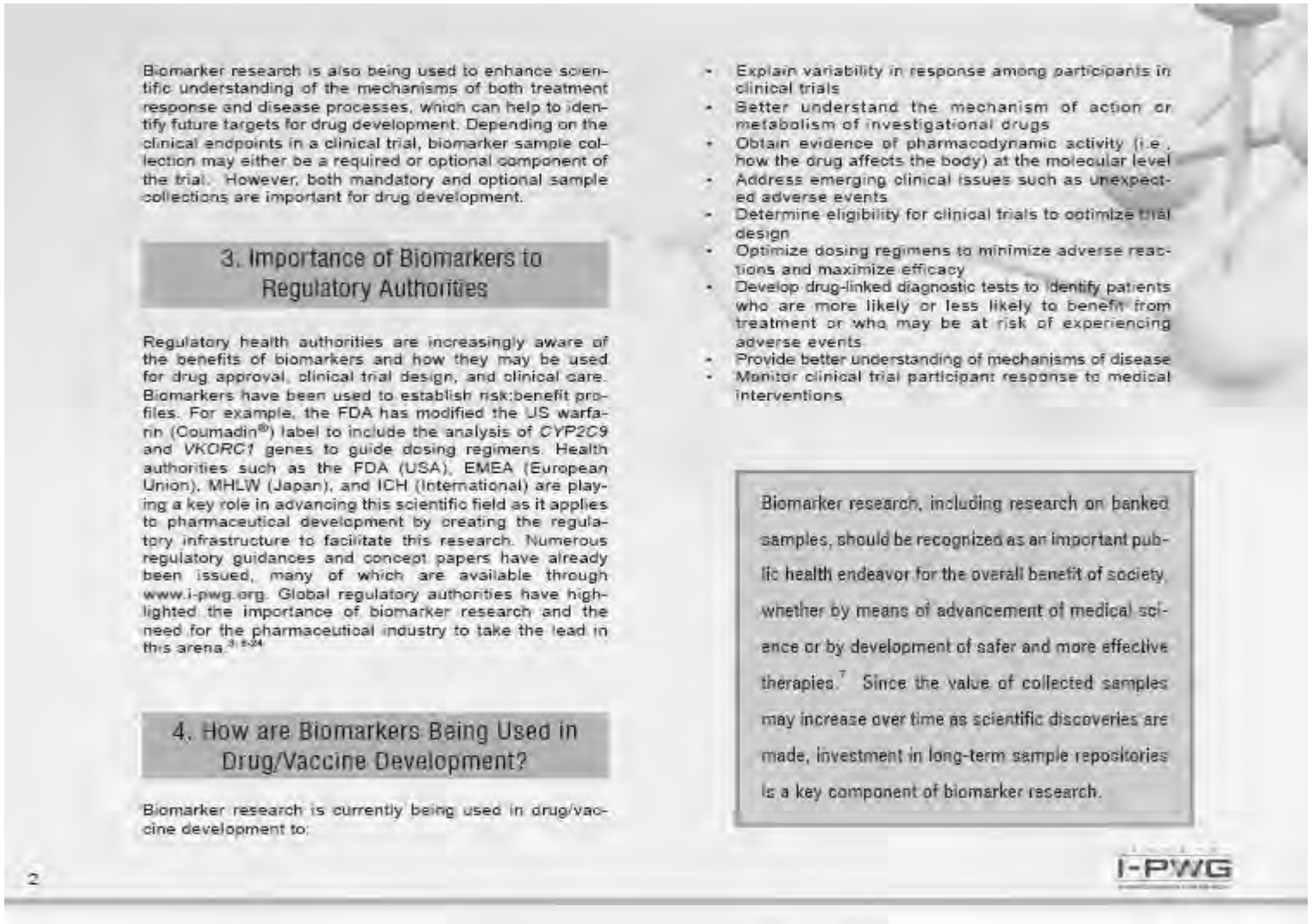

Biomarker research is also being used to enhance scientific understanding of the mechanisms of both treatment response and disease processes, which can help to identify future targets for drug development. Depending on the clinical endpoints in a clinical trial, biomarker sample collection may either 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.[3,8-24]

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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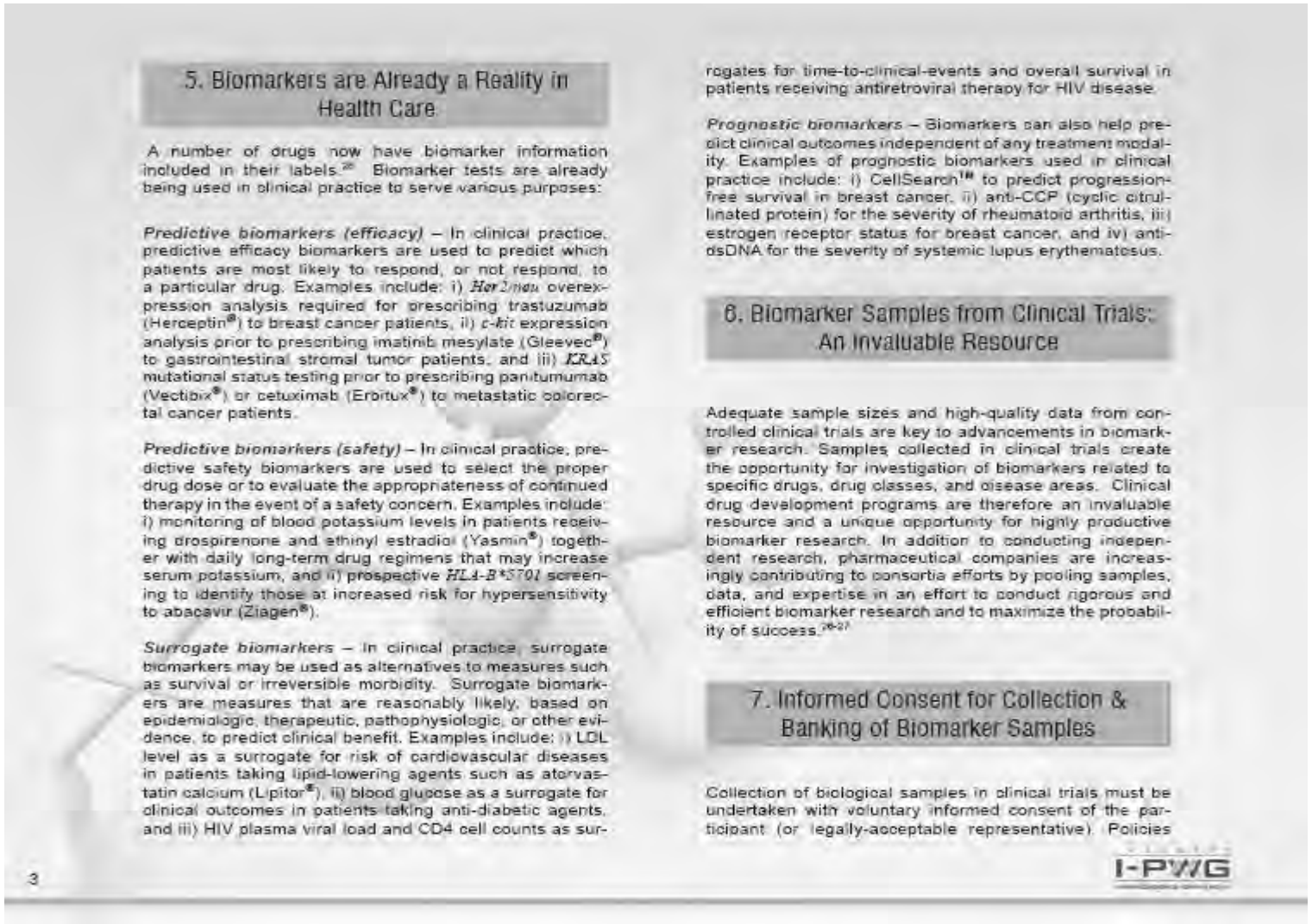

5. Biomarkers are Already a Reality in Health Care

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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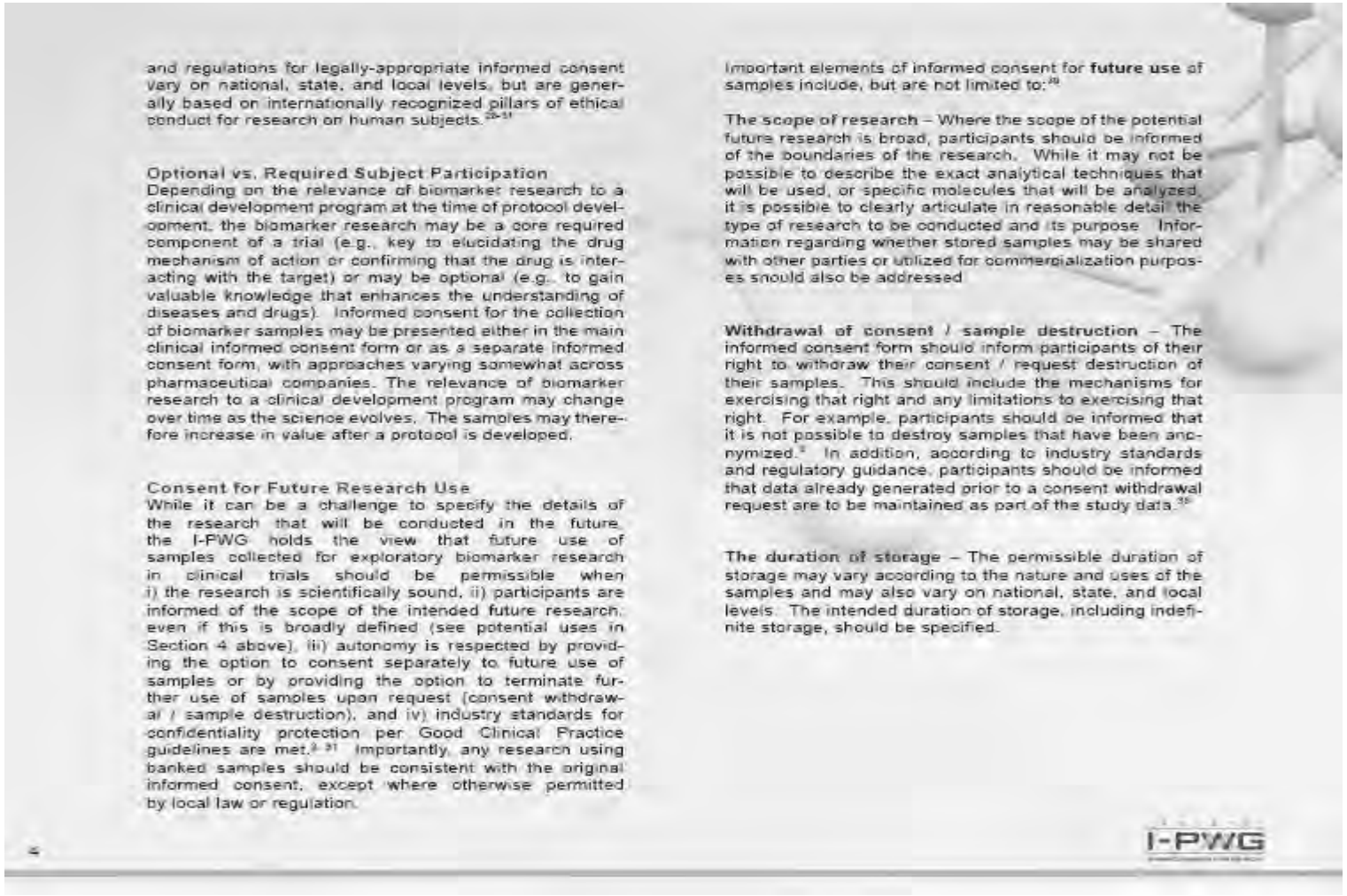


and regulations for legally-appropriate informed consent vary on national, state, and local levels, but are generally based on internationally recognized pillars of ethical conduct for research on human subjects.[28-31]

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

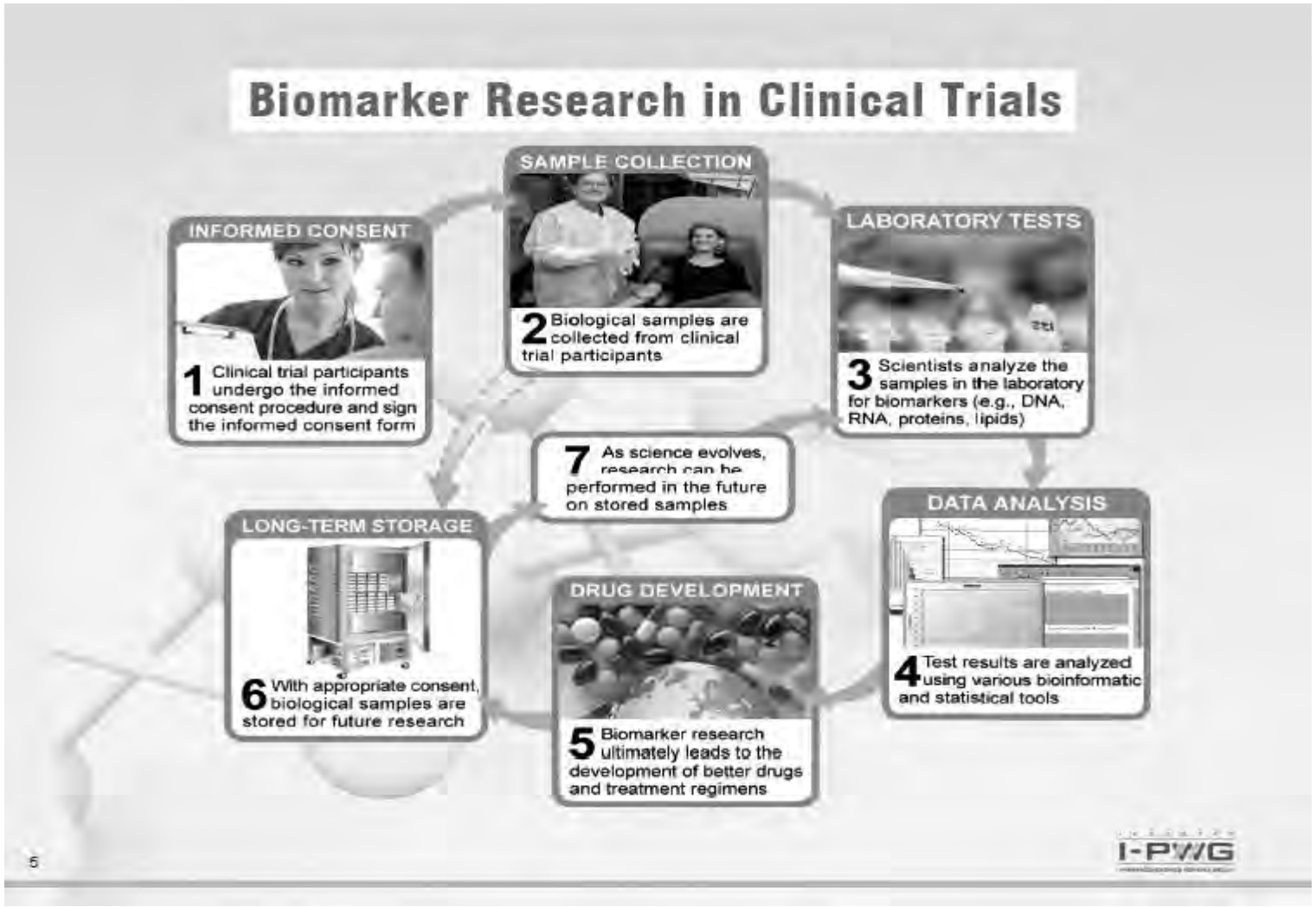
While it can be a challenge to specify the details of the research that will be conducted in the future, the I-PWG holds the view that future use of samples collected for exploratory biomarker research in clinical trials should be permissible when i) the research is scientifically sound, ii) participants 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
INFORMED CONSENT
1 Clinical trial participants undergo the informed consent procedure and sign the informed consent form
SAMPLE COLLECTION
2 Biological samples are collected from clinical trial participants
LABORATORY TESTS
3 Scientists analyze the samples in the laboratory for biomarkers (e.g., DNA, RNA, proteins, lipids)
DATA ANALYSIS
4 Test results are analyzed using various bioinformatic and statistical tools
DRUG DEVELOPMENT
5 Biomarker research ultimately leads to the development of better drugs and treatment regimens
LONG-TERM STORAGE
6 With appropriate consent, biological samples are stored for future research
7 As science evolves, research can be performed in the future on stored samples
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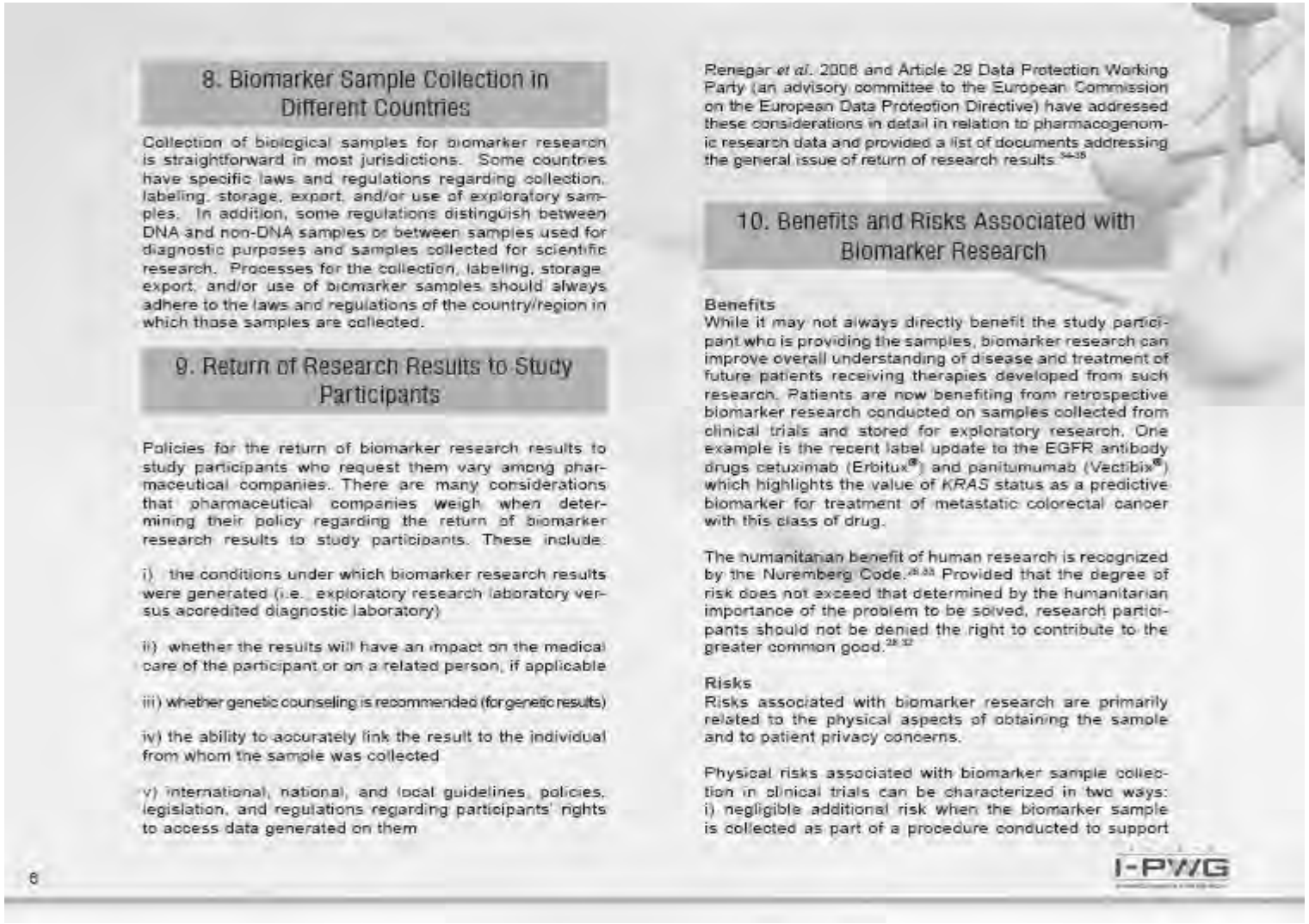

8. Biomarker Sample Collection in Different Countries

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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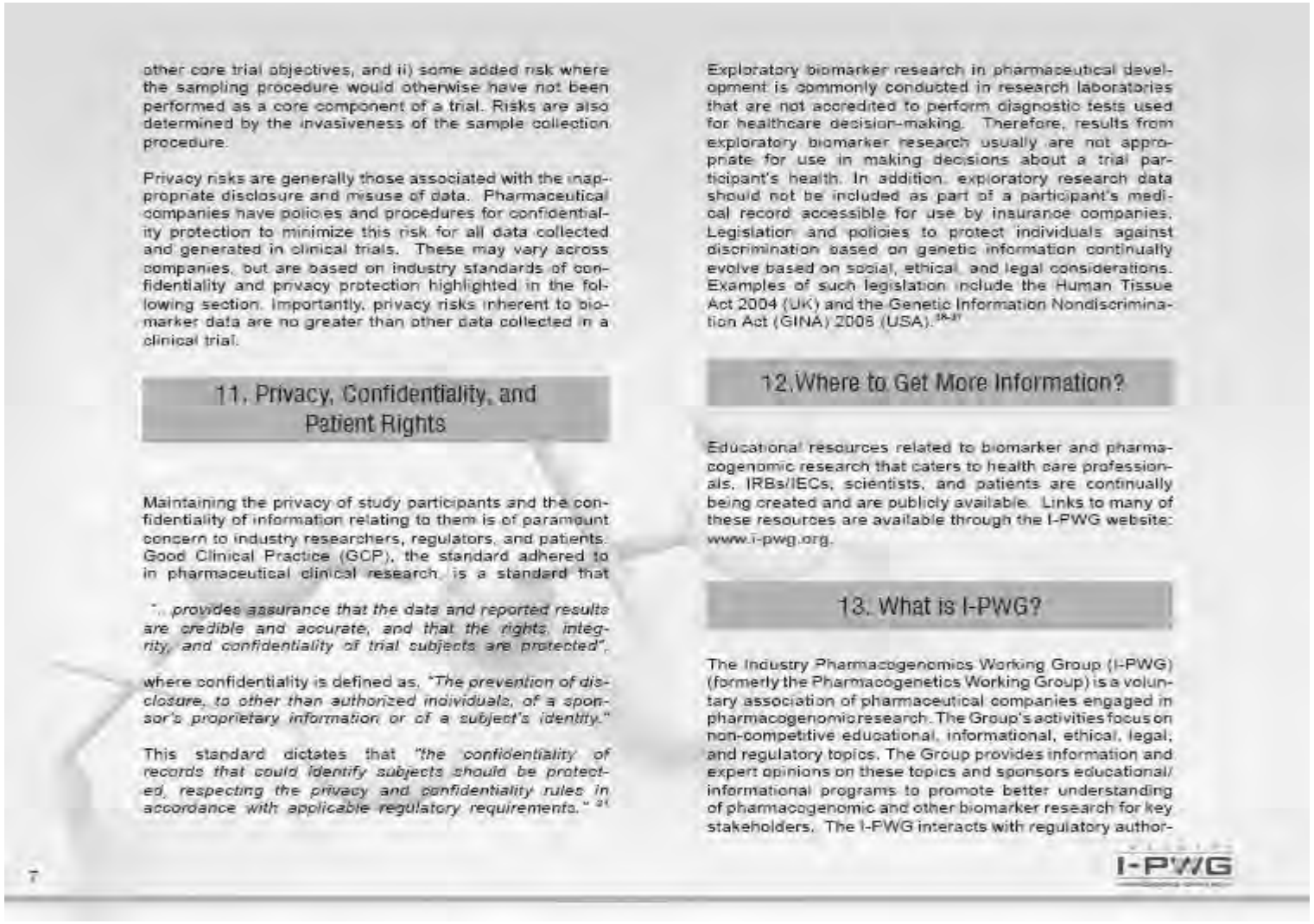

other core trial objectives, and ii) some added risk where the sampling procedure would otherwise have not been performed as a core component of a trial. Risks are also determined by the invasiveness of the sample collection procedure.

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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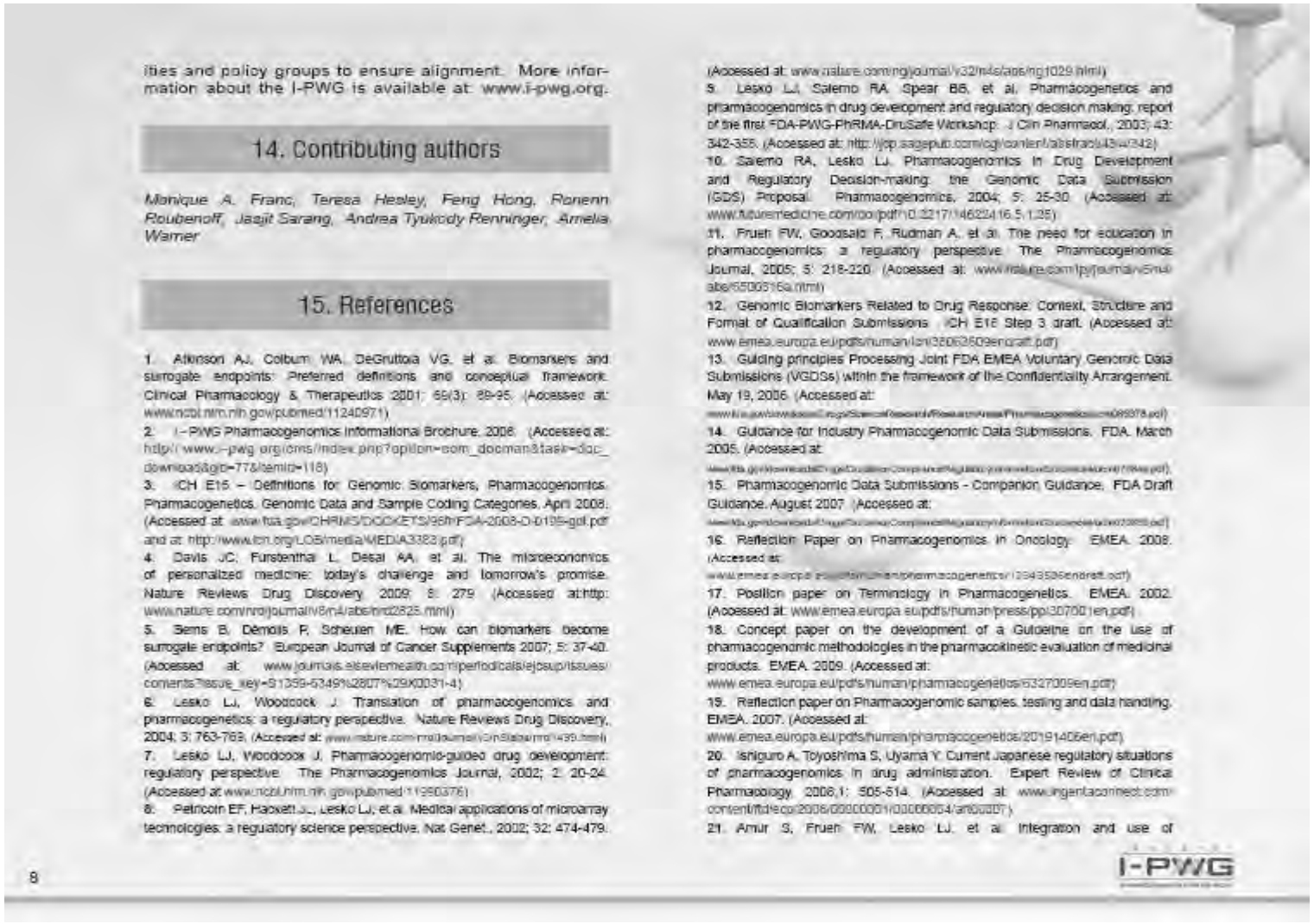

ities and policy groups to ensure alignment. More information about the I-PWG is available at: www.i-pwg.org.

14. Contributing authors

Monique A. Franc, Teresa Hesley, Feng Hong, Ronenn Roubenoff, Jasjit Sarang, Andrea Tyukody Renninger, Amelia Warner

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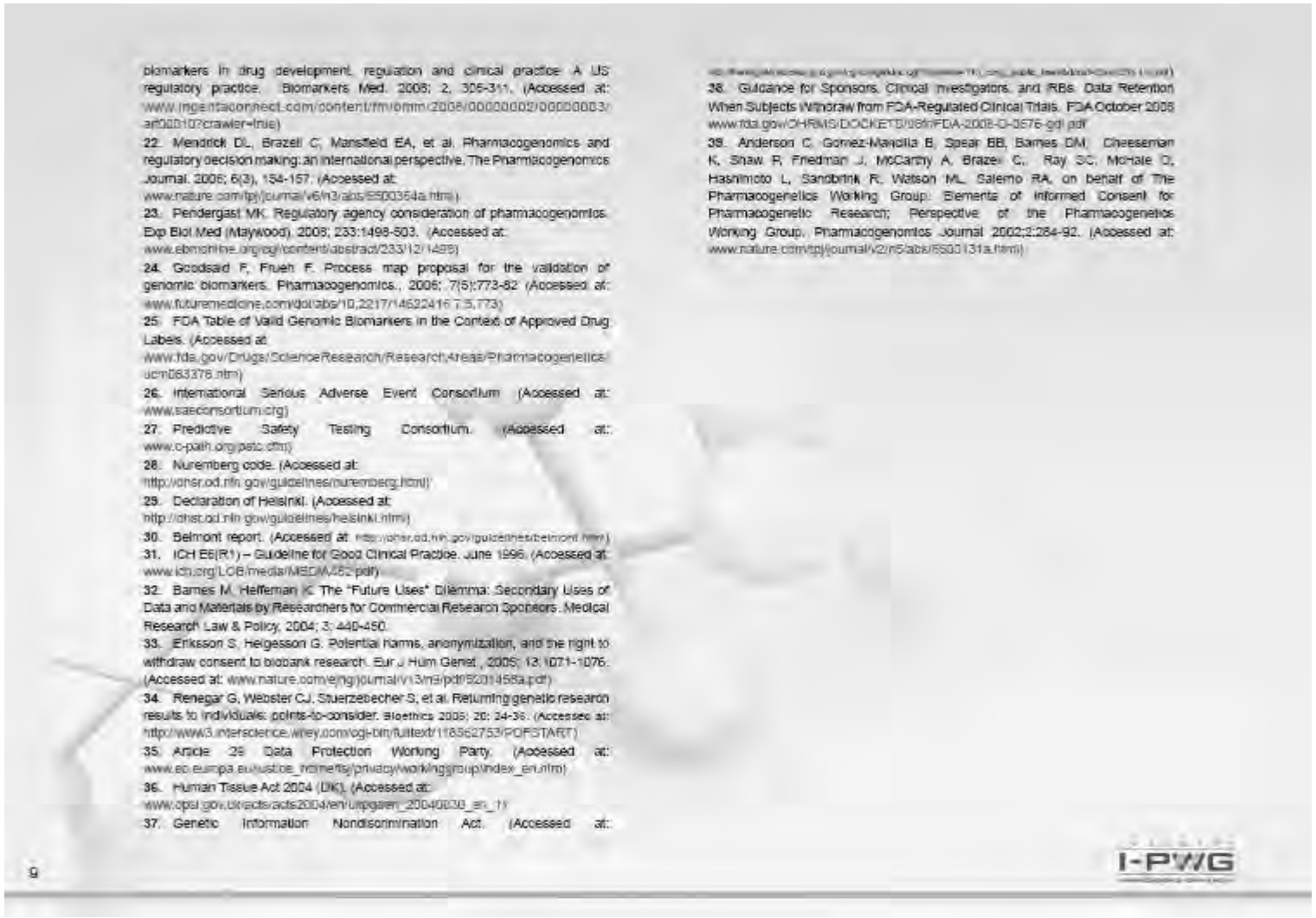

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12.4 ECOG Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. 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	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

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

12.5 Common Terminology Criteria for Adverse Events (CTCAE) version 4.0

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

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

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

* As published in the European Journal of Cancer [32].

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

Sample size = 18[a]; Target probability $p_T = 30\%$; $\varepsilon_1 = \varepsilon_2 = 0.05$.
Any doses with a dose reduction probability falling into the interval $(p_T - \varepsilon_1, p_T + \varepsilon_2)$ will be considered an acceptable dose level.

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

LEGEND

E: Stay at same dose or escalate to the next higher dose (escalation will only apply if the initial dose has been lowered, as doses higher than 800 mg/m^2 for 5-FU, 1000 mg/m^2 twice daily for capecitabine (Japan only) and 80 mg/m^2 for cisplatin will not be studied); **S**: Stay at the same dose; **D**: De-escalate to a lower dose;

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

12.8 List of Abbreviations

Abbreviation/Term	Definition
1L	First-line
3L/3L+	Third-line
5-FU	5-fluorouracil
AE	Adverse Event
ADA	Anti-Drug Antibodies
ALT	Alanine Aminotransferase
APaT/ASaT	All Patients/Subjects as Treated Population
AST	Aspartate Aminotransferase
ß-HCG	Beta Human Chorionic Gonadotropin
CBC	Complete Blood Count
CI	Confidence Interval
CIS	Carcinoma in situ
CR	Complete Response
CrCl	Calculated Creatinine Clearance
CRF	Case Report Form
CSR	Clinical Study Report
CT	Computed Tomography
CTCAE	Common Toxicity Criteria for Adverse Events
CTLA-4	Cytotoxic T-Lymphocyte-Associated Antigen-4
CTU	Computed Tomography Urography
DL	Dose Level
DLT	Dose Limiting Toxicity
DNA	Deoxyribonucleic acid
DOCR	Duration of Complete Response
ECI	Events of Clinical Interest
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organisation for Research and Treatment of Cancer
ERC	Ethics Review Committee
FAS	Full Analyses Set
FBR	Future Biomedical Research
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FDAMA	Food and Drug Administration Modernization Act
FFPE	Formalin-fixed Paraffin Embedded
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
HCV	Hepatitis C
HIV	Human Immunodeficiency Virus

Abbreviation/Term	Definition
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IHC	Immunohistochemistry
INR	International Normalized Ratio
irAEs	Immune-related Adverse Events
IRB	Institutional Review Board
ITIM	Immunoreceptor Tyrosine-based Inhibition Motif
ITSM	Immunoreceptor Tyrosine-based Switch Motif
ITT	Intent-to-Treat
IV	Intravenous
IVRS/IWRS	Interactive Voice Response System/Interactive Web Response System
KM	Kaplan-Meier
mAb	Monoclonal Antibody
mcL	Microliters
MEL	Melanoma
mg	Milligram
mg/kg	Milligram per Kilogram
mL	milliliter
MRI	Magnetic Resonance Imaging
miRNA	Micro RNA
mRNA	Messenger RNA
mTPI	Modified Toxicity Probability Interval
MSD	Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
NA or N/A	Not Applicable
NCI	National Cancer Institute
NSAID	Non-Steroidal Anti-inflammatory Drug
NSCLC	Non-small Cell Lung Cancer
ORR	Objective Response Rate
OS	Overall Survival
OTC	Over-the-counter
PBPK	Physiologically Based Pharmacokinetic
PD	Progressive Disease
PD-1	Programmed death-1
PD-L1	Programmed death-ligand 1
PFS	Progression Free Survival
PGt	Pharmacogenetic
PK	Pharmacokinetic
PK/PD	Pharmacokinetic-Pharmacodynamic
PO	Oral Administration
PR	Partial Response
RECIST	Response Evaluation Criteria in Solid Tumors

Abbreviation/Term	Definition
irRECIST	Immune-related RECIST
RNA	Ribonucleic Acid
Q2W	Every 2 Weeks
Q3W	Every 3 Weeks
SAC	Scientific Advisory Committee
SAE	Serious Adverse Events
SAP	Statistical Analysis Plan
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SOC	Standard of Care
TIL	Tumor-Infiltrating Lymphocytes
TSH	Thyroid Stimulating Hormone
ULN	Upper Limit of Normal
WHO	World Health Organization

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	

Supplemental Statistical Analysis Plan (sSAP)

1. INTRODUCTION

This supplemental SAP (sSAP) is a companion document to the protocol. In addition to the information presented in the protocol SAP which provides the principal features of confirmatory analyses for this trial, this supplemental SAP provides additional statistical analysis details/data derivations and documents modifications or additions to the analysis plan that are not "principal" in nature and result from information that was not available at the time of protocol finalization.

2. SUMMARY OF CHANGES

This is the original sSAP and thus no changes are indicated here.

3. ANALYTICAL AND METHODOLOGICAL DETAILS

3.1 Statistical Analysis Plan Summary

Key elements of the statistical analysis plan are summarized below; the comprehensive plan is provided in **Sections 3.2** to **Section 3.12**.

Study Design Overview	A Phase II Clinical Trial of Pembrolizumab as Monotherapy and in Combination with Cisplatin+5-Fluorouracil in Subjects with Recurrent or Metastatic Gastric or Gastroesophageal Junction Adenocarcinoma (KEYNOTE-059)
Treatment Assignment	Treatment assignment is open label.
Analysis Populations	Efficacy: All Subjects as Treated (ASaT) Safety: All Subjects as Treated (ASaT)
Primary Endpoint(s)	Cohort 2: Safety and tolerability (see Section 4.2.1.2) Cohort 1: objective response rate (ORR) per RECIST 1.1 assessed by central imaging vendor Cohort 3: Objective response rate (ORR) per RECIST 1.1 assessed by central imaging vendor
Statistical Methods for Key Efficacy Analyses	Cohort 1 (3L+ gastric cancer subjects/monotherapy): 95% CI for ORR will be calculated using Exact method based on binomial distribution. Cohort 2 (1L gastric cancer subjects/combination treatment): The primary objective is safety evaluation, and the secondary objective is the estimation of the ORR. 95% CI for ORR will be calculated using Exact method based on binomial distribution. Cohort 3 (1L gastric cancer subjects/monotherapy): 95% CI for ORR will be calculated using Exact method based on binomial distribution.
Statistical Methods for Key Safety Analyses	Count and percentage of AE will be provided.
Interim Analyses	For Cohort 1, an interim analysis will be performed for PD-L1 negative subjects in this study. Results will be reviewed by an external data monitoring committee. The interim analysis is summarized below. Details are provided in Section 3.7. • Interim Analysis 1: o Timing: To be performed when ~40 all-comer subjects have response assessment available o Testing: Futility check based on ORR assessed by central imaging vendor in PD-L1 negative subjects
Multiplicity	This is an estimation study. No multiplicity adjustment will be applied.
Sample Size and Power	Cohort 1 (3L+ gastric cancer subjects/monotherapy): Since the futility criterion was not met, the overall sample size for Cohort 1 is approximately 210. The enrollment of Cohort 1 will stop when at least 80 all-comer subjects meeting the revised eligibility criteria are enrolled. Cohort 2 (1L gastric cancer subjects/combination treatment): There will be approximately 18 subjects enrolled. Cohort 3 (1L gastric cancer subjects/monotherapy): There will be ~25 PD-L1 positive subjects enrolled in Cohort 3.

3.2 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.

This trial is being conducted as an open-label study. There is no randomization in the study. The Clinical Biostatistics department will generate the allocation schedule.

One planned interim analysis for Cohort 1 is described in Section 8.7. The study team will remain blinded to the PD-L1 expression level (positive or negative) for the subjects participating in the initial all-comers portion of Cohort 1 until the interim analysis of Cohort 1. Results of the interim analysis will be provided by the external unblinded statistician to the Data Monitoring Committee (DMC). The DMC will serve as the primary reviewer of the results of the interim analysis and will make recommendations in terms of whether to resume the enrollment of the PD-L1 negative subjects in Cohort 1 to the SPONSOR. Prior to study completion, the external unblinded statistician will not be involved in any discussions regarding modifications to the protocol, statistical methods, identification of protocol violators, or data validation efforts after the interim analyses. Analyses or summaries of PD-L1 biomarker status before the interim analysis will be limited and documented after the interim analysis. Following the interim analysis, the Sponsor will be unblinded to PD-L1 data.

3.3 Hypotheses/Estimation

This is an estimation study. Objectives of the study are stated in **Section 3.0**.

3.4 Analysis Endpoints

3.4.1 Efficacy Endpoints

Objective Response Rate (ORR): proportion of subjects in the analysis population who have complete response (CR) or partial response (PR).

Duration of Response (DOR): for subjects who demonstrate CR or PR, duration of response 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.

Disease Control Rate (DCR): for 1L subjects, DCR is defined as proportion of subjects in the analysis population who have CR or PR or stable disease (SD) for at least 6 months; for 3L+ subjects, DCR is defined as proportion of subjects in the analysis population who have CR or PR or stable disease (SD) for at least 2 months.

Progression-Free Survival (PFS): time from Day 1 Cycle 1 treatment administration to the first documented disease progression or death.

Overall Survival (OS): time from Day 1 Cycle 1 treatment administration to death due to any cause.

3.4.2 Safety Endpoints

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

received pembrolizumab, including serious adverse events (SAEs) and events of clinical interest (ECIs).

Safety will be assessed by reported adverse experiences using CTCAE, Version 4.0. The attribution to drug, time-of-onset, duration of the event, its resolution, and any concomitant medications administered will be recorded. AEs will be analyzed including but not limited to all AEs, SAEs, fatal AEs, and laboratory changes. Furthermore, specific immune-related adverse events (irAEs) will be collected and designated as immune-related events of clinical interest (ECIs) as described in Section 7.2.3.2.Consider referring to Section 4.2.3 for the initial description of safety measures

3.5 Analysis Populations

3.5.1 Efficacy Analysis Populations

The All Subjects as Treated (ASaT) population will be used for the analysis of ORR, DCR, PFS, and OS. ASaT population consists of all subjects who received at least one dose of study treatment.

The analysis population for DOR consists of responders.

3.5.2 Safety Analysis Populations

The All Subjects as Treated (ASaT) population will be used for the analysis of safety data in this study.

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.

3.6 Statistical Methods

3.6.1 Statistical Methods for Efficacy Analyses

In Cohorts 1 and 3, the primary endpoints are ORR per RECIST 1.1 assessed by central imaging vendor for all subjects and in PD-L1 positive subjects. The point estimate and 95% confidence interval will be provided using exact binomial method proposed by Clopper and Pearson (1934). Subjects in the primary analysis population (ASaT) without ORR data will be counted as non-responder.

In Cohort 1, the co-primary endpoint for PMDA submission is the 6-month overall survival rate (OS6) for all subjects and in PD-L1 positive subjects. The estimate of OS6 and 95% confidence interval will be provided using Kaplan-Meier method.

For DOR, Kaplan-Meier (KM) curves and median estimates from the KM curves will be provided as appropriate. Censoring rules for DOR are summarized in Table 1.

Table 1 Censoring Rules for DOR

Situation	Date of progression or censoring	Outcome
No progression nor death, no new anti-cancer therapy initiated	Last adequate assessment	Censor (non-event)
No progression nor death, new anti-cancer therapy initiated	Last adequate assessment before new anti-cancer therapy initiated	Censor (non-event)
Death or progression after ≥ 2 consecutive missed adequate disease assessments	Last adequate assessment prior to ≥ 2 missed adequate disease assessments	Censor (non-event)
Death or progression after ≤1 missed adequate disease assessments	Death or progression	End of response (Event)
Patients are considered to have an ongoing response if censored, alive, have not progressed, have not started a new anti-cancer therapy and have not been determined to be lost to follow-up.		

For each cohort, the efficacy endpoints, analysis population, and statistical methods (including missing data handling) that will be employed for the efficacy analyses are presented in Table 2.

Table 2 Summary of Analysis Strategy for Efficacy Endpoints

Endpoint	Statistical Method	Analysis Population	Missing data approach
ORR • RECIST 1.1, central imaging vendor • RECIST 1.1, investigator • irRECIST 1.1, central imaging vendor	Exact method based on binomial distribution	FAS in all below populations: Cohort 1* • all • PD-L1+ Cohort 2 • all • PD-L1+ Cohort 3 (PD-L1+ only)	Subjects with missing data are considered non-responders
OS	Summary statistics using Kaplan-Meier method	ASaT in all below populations: Cohort 1 • all • PD-L1+ Cohort 2 • all • PD-L1+ Cohort 3 (PD-L1+ only)	Censored at last assessment date
DCR • RECIST 1.1, central imaging vendor • RECIST 1.1, investigator • irRECIST 1.1, central imaging vendor	Exact method based on binomial distribution	ASaT in all below populations: Cohort 1 • all • PD-L1+ Cohort 2 • all • PD-L1+ Cohort 3 (PD-L1+ only)	Subjects with missing data are considered as disease not under control
PFS • RECIST 1.1, central imaging vendor • RECIST 1.1, investigator • irRECIST 1.1, central imaging vendor	Summary statistics using Kaplan-Meier method	ASaT in all below populations: Cohort 1 • all • PD-L1+ Cohort 2 • all • PD-L1+ Cohort 3 (PD-L1+ only)	Censored at last assessment date
DOR • RECIST 1.1, central imaging vendor • RECIST 1.1, investigator • irRECIST 1.1, central imaging vendor	Summary statistics using Kaplan-Meier method	Responders in all below populations: Cohort 1 • all • PD-L1+ Cohort 2 • all • PD-L1+ Cohort 3 (PD-L1+ only)	Censored at last assessment date
HRQOL assessments	Summary statistics	ASaT in all below populations: Cohort 1 • all • PD-L1+ Cohort 2 • all • PD-L1+ Cohort 3 (PD-L1+ only)	Missing data will not be included in summary

* In Cohort 1, ORR per RECIST 1.1 assessed by central imaging vendor for all subjects and in PD-L1+ subjects is considered primary; all other efficacy analyses are considered supportive.

3.6.2 Statistical Methods for Safety Analyses

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

3.6.3 Summaries of Baseline Characteristics, and Demographics

The number and percentage of subjects screened, enrolled, the primary reasons for screening failure, and the primary reason for discontinuation will be displayed. Demographic variables, baseline characteristics, primary and secondary diagnoses, and prior and concomitant therapies will be summarized by treatment either by descriptive statistics or categorical tables.

3.7 Interim Analyses

For Cohort 1, an interim analysis will be performed for PD-L1 negative subjects. The endpoint, timing, and purpose of the interim analyses are summarized in Table 3.

The detailed process is described as below:

1. Enrollment will begin with an all-comer population. After both the PD-L1 assay is ready and ~40 all-comers enrolled, enrollment of PD-L1 positive subjects will be continued, and PD-L1 negative subject enrollment will be paused.

2. An interim analysis (reviewed by external DMC) will be performed when the initially enrolled all-comers (n~40) have response assessment available. The purpose of this interim analysis is to check treatment futility on the PD-L1 negative subjects. It is estimated that approximately 25 PD-L1 negative subjects will be included in this interim analysis.

3. If the futility criterion is not met, the PD-L1 negative subject enrollment will be resumed. The trial enrollment will end when at least 80 all-comer subjects meeting the revised eligibility criteria are enrolled. If the futility criterion is met for the PD-L1 negative subjects, the trial will continue to only enroll PD-L1 positive subjects until there are at least 90 PD-L1 positive subjects.

For the PD-L1 negative subjects, the futility criterion is met if the upper bound of the 95% confidence interval of ORR is less than 20%. If the futility criterion is met then the enrollment of PD-L1 negative subjects will not be resumed.

Among the initially enrolled ~40 all-comers, the actual number of PD-L1 negative subjects could vary depending on prevalence rate. According to the futility rule defined above, if 25 PD-L1 negative subjects are included in the interim analysis, and if no responder is observed, enrollment of PD-L1 negative subjects in Cohort 1 will not resume. Otherwise, if 1 or more responders are observed among the 25 PD-L1 negative subjects, the enrollment of the PD-L1 negative subjects will be re-opened.

Table 3: Summary of Interim Analysis Strategy

Key Endpoints for Interim Analysis	Timing of Interim Analysis	Purpose of Interim Analysis
ORR (confirmed or unconfirmed) By RECIST 1.1,central imaging vendor assessment	Initially enrolled ~40 all-comers have response assessment available (~25 PD-L1 negative subjects provided)	Check futility for PD-L1 negative subjects

As of Oct 19, 2015, an interim analysis has been performed and the external DMC has reviewed the data. The futility criterion was not met and the DMC recommended that the enrollment of PD-L1 negative subjects could be resumed.

3.8 Multiplicity

This is an estimation study. 95% confidence intervals of ORR will be provided. No multiplicity adjustment will be applied.

3.9 Sample Size and Power Calculations

Cohort 1 (3L+ gastric cancer subjects/monotherapy):

- Enrollment began with an all-comer population. By 23 July 2015, 42 all-comer subjects were enrolled and included in the interim analysis.
- Then only PD-L1 positive subjects were enrolled until the outcome of the interim analysis was determined on 19 October 2015. From 23 July 2015 to 19 October 2015, approximately 33 PD-L1 positive subjects were enrolled.
- Since the futility criterion was not met at the interim analysis, the enrollment of PD-L1 negative subjects will resume. Enrollment after the interim analysis will not stop until at least 80 all-comer subjects meeting the revised eligibility criteria are enrolled. Since the implementation of the amendment takes time, it is estimated that approximately 135 all-comer subjects will be enrolled after the interim analysis, including about 55 all-comer subjects enrolled under the original protocol and 80 under the amendment.

Thus, it is estimated that the overall sample size for Cohort 1 is approximately 210.

Table 4 shows the two-sided 95% CI of ORR with 90 evaluable subjects for different observed response rates. With 90 PD-L1 positive subjects, if there are at least 16 responders observed, the lower bound of the 95% confidence interval for ORR will be above 10%.

Table 4 Two-sided 95% CI of ORR with 210 Subjects

Number of observed responders	ORR estimates	95% CI of ORR (%)
30	14.3%	(9.9, 19.8)
31	14.8%	(10.3, 20.3)
32	15.2%	(10.7, 20.8)
33	15.7%	(11.1, 21.4)

Assuming the prevalence of PD-L1 positive is 50% based on the interim analysis and ~33 PD-L1 positive subjects are enrolled during the period of enrolling only PD-L1 positive subjects; there will be a total of approximately 120 PD-L1 positive subjects in Cohort 1. Table 5 shows the two-sided 95% CI of ORR with 120 PD-L1 positive subjects for different response rates.

Table 5 Two-sided 95% CI of ORR with 120 PD-L1 Positive Subjects

Number of observed responders	ORR estimates	95% CI of ORR (%)
19	15.8%	(9.8, 23.6)
20	16.7%	(10.5, 24.6)
21	17.5%	(11.2, 25.5)
22	18.3%	(11.9, 26.4)

Table 6 shows the two-sided 95% CI of ORR with 80 all-comer subjects meeting the revised eligibility criteria for different observed response rates.

Table 6 Two-sided 95% CI of ORR with 80 Subjects Meeting Revised Eligibility Criteria

Number of observed responders	ORR estimates	95% CI of ORR (%)
14	17.5%	(9.9, 27.6)
15	18.8%	(10.9, 29.0)
16	20.0%	(11.9, 30.4)
17	21.3%	(12.9, 31.8)

Cohort 2 (1L gastric cancer subjects/combination treatment): There will be approximately 18 subjects enrolled for all-comer population. Table 7 shows the two-sided 95% CI of AE rate with 18 subjects.

Table 7 Two-sided 95% CI of AE incidence rate with 18 Subjects

Number of AE	AE incidence rate estimates	95% CI of incidence rate (%)
2	11.1%	(1.4, 34.7)
4	22.2%	(6.4, 47.6)
5	27.7%	(9.7, 53.5)
7	38.9%	(17.3, 64.2)
9	50.0%	(26.0, 73.9)

Cohort 3 (1L gastric cancer subjects/monotherapy): There will be ~25 PD-L1 positive subjects enrolled in Cohort 3. Using Bayesian sample size methods and assuming a uniform prior for the response rate (beta-binomial prior with beta (1, 1)), if we observe no more than 8 responders (i.e. observed ORR <=32%), there is >= 77% posterior probability that the true ORR is less than 40% (ORR from Standard of Care).

3.10 Subgroup Analyses and Effect of Baseline Factors

Efficacy analyses will be performed within the following subgroups:

- Subjects classified based on PD-L1 biomarker status as appropriate;
- Subjects in Cohort 1 meeting the revised eligibility criteria.

3.11 Compliance (Medication Adherence)

Drug accountability data for MK-3475 will be collected during the study. Any deviation from protocol-directed administration will be reported.

3.12 Extent of Exposure

Extent of Exposure for a subject is defined as number of cycles in which the subject receives the study medication infusion. Summary statistics will be provided on Extent of Exposure for ASaT population.