Official Protocol Title:	Phase IB Study of Pembrolizumab (MK-3475) in Subjects with Select Advanced Solid Tumors
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TITLE:

Phase IB Study of Pembrolizumab (MK-3475) in Subjects with Select Advanced Solid Tumors

IND NUMBER: 110,080
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SUMMARY OF CHANGES

PRIMARY REASON(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
5.2.1.2	Dose Modification and Toxicity Management Guidelines for Pembrolizumab	Table 3: Addition of Myocarditis as a table row and specific actions for Grades 2, 3, and 4 to the dose modification table.	To clarify dose modification for myocarditis - Program-wide safety update to program language
7.1.5.4.1	Survival Follow-up	Change of subheading to Survival Status. Addition of paragraph to enable survival follow-up activities throughout the study. Removal of redundant text.	Program-wide update - to allow flexibility in the entire follow-up period beyond the current Survival Follow-up portion and to enable more frequent follow-ups as necessary
6.1 and 6.2	Study Flow Charts	Merging of cells for survival status to allow continual monitoring throughout the study.	

ADDITIONAL CHANGE(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
1.0	Trial Summary	Updated with program language to include reference to the extension study.	To allow for continued provision of pembrolizumab to subjects with appropriate risk-benefit assessment
2.2	Trial Diagram	Updated to include extension study.	
5.10	Beginning and End of the Trial	Updated with program language to include reference to the extension study.	
5.1.2	Subject Inclusion Criteria	Criteria 4 – insertion of "one" to "Have one of the following advanced (unresectable and/or metastatic) solid tumor indications:"	To correct an erroneous deletion made in the previous amendment
5.2.1.2 5.6.1 5.6.1.1 7.1.2.1	Dose Modification and Toxicity Management Guidelines for Pembrolizumab Supportive Care Guidelines Supportive Care Guidelines for Events of Clinical Interest and Immune-related Adverse Events (irAEs) Adverse Event (AE) Monitoring	Removed cross reference to retired ECI guidance document.	To align with program language

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
7.2.3.2 8.1.2 8.2.3.2 8.2.5.2	Events of Clinical Interest Safety Analyses Safety Endpoints Statistical Methods for Safety Analysis		
6.1 and 6.2 7.1.2.5.1 7.1.2.5.4 7.1.2.5.5 7.1.5.4	Study Flow Charts Assessment of Disease End of Treatment and Follow-up Tumor Imaging Second Course (Retreatment) Tumor Imaging Follow-up Visits	Schedule of imaging/visits in the 1st course phase follow-up period extended from every 8 weeks to every 12 weeks after Month 6. In the second course phase imaging frequency extended to every 12 weeks throughout.	To reduce the burden on subjects
6.0 7.1.2.7	Trial Flow Chart Tumor Marker Assessment (Optional)	In 6.1 and 6.2: footnote #j and q, and Section 7.1.2.7: Removed the timing of tumor marker data collection and clarified that data collection will occur at the same time as post-treatment imaging	To increase clarity following changes to follow-up imaging schedule
12.5	Common Terminology Criteria for Adverse Events V4.0 (CTCAE)	The nonfunctioning website link to CTCAE V4.0 updated to a functioning link	To provide a functioning website link

1.0 TRIAL SUMMARY

Abbreviated Title	Pembrolizumab (MK-3475 [SCH 900475]) Solid All Comers
Trial Phase	1B
Clinical Indication	The treatment of subjects with any of the following advanced (unresectable and/or metastatic) solid tumor indications: A1 Colon or Rectal Adenocarcinoma A2 Anal Canal Squamous Cell Carcinoma A3 Pancreas Adenocarcinoma A4 Esophageal Squamous Cell Carcinoma or Adenocarcinoma (Including GE Junction) A5 Biliary Tract Adenocarcinoma (Gallbladder and Biliary Tree but excluding Ampulla of Vater Cancers) A6 Carcinoid Tumors A7 Neuroendocrine Carcinomas (Well or moderately differentiated Pancreatic Neuroendocrine Tumor) B1 ER Positive HER2 Negative Breast Cancer B2 Ovarian Epithelial, Fallopian Tube or Primary Peritoneal Carcinoma B3 Endometrial Carcinoma B4 Cervical Squamous Cell Cancer B5 Vulvar Squamous Cell Carcinoma C1 Small Cell Lung Cancer C2 Mesothelioma (Malignant Pleural Mesothelioma) D1 Thyroid Cancer (Papillary or Follicular Subtype) D2 Salivary Gland Carcinoma D3 Nasopharyngeal Carcinoma E1 Glioblastoma Multiforme E2 Leiomyosarcoma E3 Prostate Adenocarcinoma
Trial Type	Interventional
Type of control	No treatment control
Route of administration	Intravenous
Trial Blinding	Unblinded Open-label
Treatment Groups	Pembrolizumab 10 mg/kg IV every 2 weeks (Q2W)
Number of trial subjects	Approximately 440 subjects will be enrolled.
Estimated duration of trial	The sponsor estimates that the trial will require approximately 24 months from the time the first subject signs the informed consent until the last subject's last visit.
Duration of Participation	Each subject will participate in the trial from the time the subject signs the Informed Consent Form (ICF) through the final protocol-specified contact. After a screening phase of 28 days, eligible subjects will receive treatment on Day 1 of each 2-week dosing cycle. Treatment with MK-3475 will continue until documented confirmed disease progression, unacceptable adverse event(s), intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw the subject, subject withdraws consent, pregnancy of the subject,

	noncompliance with trial treatment or procedure requirements; subject receives 24 months of study medication, or administrative reasons. Subjects who attain a complete response may consider stopping trial treatment if they meet criteria for holding therapy. Subjects who stop trial treatment after receiving 24 months of study medication for reasons other than disease progression or intolerability or who attain a complete response and stop trial treatment may be eligible for up to 1 year of retreatment after experiencing disease progression. The decision to retreat will be at the discretion of the investigator only if they meet the criteria for retreatment and the trial is ongoing. After the end of treatment, each subject will be followed for 30 days for adverse event (AE) monitoring (serious adverse events [SAEs] will be collected for 90 days after the end of treatment). Subjects who discontinue for reasons other than disease progression will have post-treatment follow-up for disease status until disease progression, initiating a non-study cancer treatment, withdrawing consent, or becoming lost to follow-up. All subjects will be followed by telephone for overall survival until death, withdrawal of consent, or the end of the study. Once the subject has achieved the study objective or study has ended, the subject is discontinued from this study and will be enrolled in an extension study to continue protocol defined assessments and treatment.

A list of abbreviations used in this document can be found in Section 12.9.

2.0 TRIAL DESIGN

2.1 Trial Design

This is a multicenter, nonrandomized, multi-cohort trial of pembrolizumab (MK-3475) in subjects with Programmed Death - Ligand 1 (PD-L1) positive advanced solid tumors. Subjects will be enrolled into 1 of the following 20 solid tumor cohorts:

A1 Colon or Rectal Adenocarcinoma
A2 Anal Canal Squamous Cell Carcinoma
A3 Pancreas Adenocarcinoma
A4 Esophageal Squamous Cell Carcinoma or Adenocarcinoma (Including GE Junction)
A5 Biliary Tract Adenocarcinoma (Gallbladder and Biliary Tree but excluding Ampulla of Vater Cancers)
A6 Carcinoid Tumors
A7 Neuroendocrine Carcinomas (Well or moderately differentiated Pancreatic Neuroendocrine Tumor)

B1 ER Positive HER2 Negative Breast Cancer
B2 Ovarian Epithelial, Fallopian Tube or Primary Peritoneal Carcinoma
B3 Endometrial Carcinoma
B4 Cervical Squamous Cell Cancer
B5 Vulvar Squamous Cell Carcinoma

C1 Small Cell Lung Cancer
C2 Mesothelioma (Malignant Pleural Mesothelioma)

D1 Thyroid Cancer (Papillary or Follicular Subtype)
D2 Salivary Gland Carcinoma
D3 Nasopharyngeal Carcinoma

E1 Glioblastoma Multiforme
E2 Leiomyosarcoma
E3 Prostate Adenocarcinoma

Approximately 440 subjects will be enrolled in this trial to examine the safety and efficacy in these cohorts to the 10 mg/kg dose of pembrolizumab administered every 2 weeks. Subjects will be evaluated every 8 weeks (56 days ±7 days) with radiographic imaging to assess response to treatment. After 6 months, radiography imaging will be evaluated every 12 weeks (84 days ±7 days). Response evaluation criteria in solid tumors (RECIST) 1.1 will be used as the primary efficacy endpoint of response rate.

RECIST 1.1 will be adapted as described in Section 4.2.3.1 due to the tumor response patterns seen with pembrolizumab treatment (e.g., tumor flare), and this adapted RECIST will be used by the sites for treatment decisions. Adverse events (AEs) will be monitored throughout the trial and graded in severity according to the guidelines outlined in the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Treatment with pembrolizumab will continue until documented disease progression, unacceptable AEs, intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw the subject, subject withdraws consent, pregnancy of the subject, noncompliance with trial treatment or procedure requirements, completion of 24 months of treatment with pembrolizumab, or administrative reasons. Subjects who attain an investigator-determined confirmed complete response (CR) may consider stopping trial treatment after receiving at least 24 weeks of treatment. In addition, subjects who discontinue after at least 24 months of therapy for reasons other than disease progression or intolerability, or who discontinue after attaining a CR and had at least 2 treatments beyond initial CR, may be eligible for up to 1 year of retreatment if they subsequently experience 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 7.1.5.2.1 for further details). After the end of treatment, each subject will be followed for 30 days for adverse event monitoring (serious adverse events will be collected for 90 days after the end of treatment). Subjects who discontinue treatment for reasons other than disease progression will have post-treatment follow-up of disease status until disease progression, initiating a non-study cancer treatment, withdrawing consent, or becoming lost to follow-up. All subjects will be followed by telephone contact for overall survival (OS) until death, withdrawal of consent or the end of the study, whichever comes first.

The primary objective of the trial is to evaluate a preliminary signal of potential anti-tumor activity of pembrolizumab in subjects with PD-L1 positive advanced solid tumors. Secondary objectives include safety and tolerability, progression-free survival (PFS), OS and response duration.

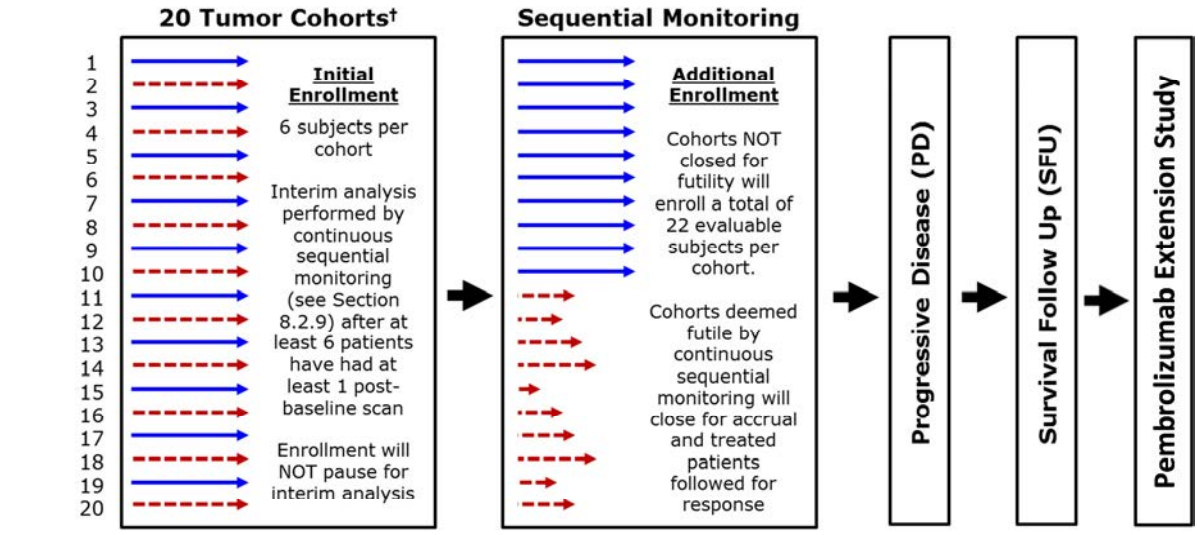
Participation in this trial will be dependent upon supplying tissue from an archival tissue sample or newly obtained biopsy of a tumor lesion not previously irradiated (tumors progressing in a prior site of radiation are allowed for PD-L1 characterization, other exceptions may be considered after Sponsor consultation). This specimen will be evaluated at a central laboratory for expression status of PD-L1 by immunohistochemistry (IHC). Only subjects with PD-L1 positive tumors will be enrolled in the trial.

This study will be conducted in conformance with Good Clinical Practices (GCP)s.

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

2.2 Trial Diagram

The trial design is depicted in Figure 1.



† List of 20 Advanced Solid Tumor Indication for which No Curative Therapy Exists:

A1 Colon or Rectal Adenocarcinoma
A2 Anal Canal Squamous Cell Carcinoma
A3 Pancreas Adenocarcinoma
A4 Esophageal Squamous Cell Carcinoma or Adenocarcinoma (Including GE Junction)
A5 Biliary Tract Adenocarcinoma (Gallbladder and Biliary Tree but excluding Ampulla of Vater Cancers)
A6 Carcinoid Tumors
A7 Neuroendocrine Carcinomas (Well or moderately differentiated Pancreatic Neuroendocrine Tumor)

B1 ER Positive HER2 Negative Breast Cancer
B2 Ovarian Epithelial, Fallopian Tube or Primary Peritoneal Carcinoma
B3 Endometrial Carcinoma
B4 Cervical Squamous Cell Cancer
B5 Vulvar Squamous Cell Carcinoma

C1 Small Cell Lung Cancer
C2 Mesothelioma (Malignant Pleural Mesothelioma)

D1 Thyroid Cancer (Papillary or Follicular Subtype)
D2 Salivary Gland Carcinoma
D3 Nasopharyngeal Carcinoma

E1 Glioblastoma Multiforme
E2 Leiomyosarcoma
E3 Prostate Adenocarcinoma

Figure 1 Trial Design

3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

3.1 Primary Objective(s) & Hypothesis(es)

(1) **Objective:** To evaluate preliminary signals of potential anti-tumor activity of pembrolizumab in subjects with a given histopathologic type of PD-L1 positive advanced solid tumor based on RECIST 1.1 as determined by the investigator in the tumor indications below.

Hypotheses: Intravenous administration of single agent pembrolizumab to subjects with a given PD-L1 positive solid tumor type will result in a clinically meaningful best overall response rate (ORR) greater than 10% based on RECIST 1.1 criteria.

The primary objective will be tested separately in each tumor indication listed below:

A1 Colon or Rectal Adenocarcinoma
A2 Anal Canal Squamous Cell Carcinoma
A3 Pancreas Adenocarcinoma
A4 Esophageal Squamous Cell Carcinoma or Adenocarcinoma (Including GE Junction)
A5 Biliary Tract Adenocarcinoma (Gallbladder and Biliary Tree but excluding Ampulla of Vater Cancers)
A6 Carcinoid Tumors
A7 Neuroendocrine Carcinomas (Well or moderately differentiated Pancreatic Neuroendocrine Tumor)

B1 ER Positive HER2 Negative Breast Cancer
B2 Ovarian Epithelial, Fallopian Tube or Primary Peritoneal Carcinoma
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C1 Small Cell Lung Cancer
C2 Mesothelioma (Malignant Pleural Mesothelioma)

D1 Thyroid Cancer (Papillary or Follicular Subtype)
D2 Salivary Gland Carcinoma
D3 Nasopharyngeal Carcinoma

E1 Glioblastoma Multiforme
E2 Leiomyosarcoma
E3 Prostate Adenocarcinoma

3.2 Secondary Objective(s) & Hypothesis(es)

Across-Indication Secondary Objective

(1) **Objective:** To determine the safety and tolerability of pembrolizumab across selected PD-L1 positive advanced solid tumors.

Within-Indication Secondary Objectives

The following secondary objectives will be evaluated separately in each of the 20 disease indications listed in Section 3.1.

(1) **Objective**: To evaluate the PFS in subjects with a given PD-L1 positive advanced solid tumor type receiving pembrolizumab.

(2) **Objective**: To evaluate the OS in subjects with a given PD-L1 positive advanced solid tumor type receiving pembrolizumab.

(3) **Objective**: To evaluate the duration of response (DOR) in subjects with a given PD-L1 positive advanced solid tumor type receiving pembrolizumab.

3.3 Exploratory Objective

Across-Indication Exploratory Objectives

The following exploratory objectives will be evaluated across all 20 disease indications:

(1) **Objective:** To evaluate potential anti-tumor activity of pembrolizumab in subjects with a given immune signature

(2) **Objective**: To investigate the relationship between other candidate efficacy/resistance biomarkers and anti-tumor activity of pembrolizumab utilizing tumor tissue and blood sampling.

Within-Indication Exploratory Objectives

The following exploratory objectives will be evaluated separately for each of the 20 disease indications listed in Section 3.1:

(1) **Objective**: To evaluate the anti-tumor activity of pembrolizumab in subjects with a given PD-L1 positive advanced solid tumor type using continuous tumor measurements.

(2) **Objective**: To explore the relationship between PD-L1 continuous IHC scale score and anti-tumor activity of pembrolizumab in subjects with a given advanced solid tumor type.

(3) **Objective (optional)**: To evaluate the anti-tumor activity of pembrolizumab in subjects with a given PD-L1 positive advanced solid tumor type based on RECIST 1.1 as determined by central radiology review, response assessment in neuro-oncology (RANO) criteria for the glioblastoma multiforme (GBM) cohort, and Prostate Cancer Clinical Trials Working Group 2 (PCWG2) for the prostate cancer cohort.

4.0 BACKGROUND & RATIONALE

4.1 Background

Refer to the Investigator's Brochure for detailed background information on pembrolizumab/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 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 programmed cell death 1 [PDCD1]) is an immunoglobulin (Ig) superfamily member related to clusters of differentiation 28 (CD28) and cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) [7] [8]. The structure of murine PD-1 has been resolved [9]. PD-1 and family members are type I transmembrane glycoproteins containing an Ig Variable-type (V-type) domain responsible for ligand binding and a cytoplasmic tail which is responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif 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 zeta-chain-associated protein kinase (ZAP70) which are involved in the CD3 T-cell signaling cascade [7] [10] [11] [12]. The mechanism by which PD-1 down modulates T-cell responses is similar to, but distinct from that of CTLA-4 as both molecules regulate an overlapping set of signaling proteins [13] [14]. PD-1 was shown to be expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B-cells, T regs and Natural Killer cells [15] [16]. Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells [17]. The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types, including non-hematopoietic tissues as well as in various tumors [18] [19] [20] [13]. Both ligands are type I transmembrane receptors containing both immunoglobulin variable domain (IgV) and immunoglobulin constant domain (IgC)like domains in the extracellular region and contain short cytoplasmic regions with no known signaling motifs. Binding of either PD-1 ligand to PD-1 inhibits T-cell activation triggered through the T-cell receptor. PD-L1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory

environments. PD-L2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T-cell function in peripheral tissues [13]. Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. PD-1 has been suggested to regulate tumor-specific T-cell expansion in subjects with melanoma (MEL) [21]. This suggests that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention.

Pembrolizumab (previously known as SCH 900475) 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.

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, MEL and colorectal carcinoma. Blockade of the PD-1 pathway effectively promoted CD8+ T-cell infiltration into the tumor and the presence of interferon gamma, granzyme B and perforin, indicating that the mechanism of action involved local infiltration and activation of effector T-cell function in vivo [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 Investigator's Brochure).

4.1.3 Ongoing Clinical Trials

Ongoing clinical trials are being conducted in advanced melanoma, non-small cell lung cancer, head and neck cancer, urothelial cancer, triple negative breast cancer, gastric cancer and hematologic malignancies. For study details please refer to the Investigator's Brochure.

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

Details regarding specific benefits and risks for subjects participating in this clinical trial may be found in the accompanying Investigators Brochure and Informed Consent documents.

This is a multicenter, nonrandomized, multi-cohort trial of pembrolizumab in PD-L1 positive subjects with advanced solid tumors. Subjects will be enrolled into 1 of 20 solid tumor indications as outlined in Section 2.1. Given that immune checkpoints such as the PD-1/PD-L1 axis may be relevant in a variety of solid tumors in addition to the ones previously studied, exploration as to which of these tumors might be more responsive to PD-1 inhibition is being pursued in this protocol. Twenty indications with a significant unmet medical need in the metastatic/refractory setting for which there is internal PD-1/PD-L1 data were chosen

for study. This indication discovery effort may lead to a better understanding of which tumor types may be more responsive to pembrolizumab.

Participation in this trial will be dependent upon supplying tissue from an archival tissue sample or newly obtained core or excisional biopsy of a tumor lesion to evaluate for PD-L1 expression by IHC. If an archival specimen is PD-L1 negative but a newly obtained biopsy is positive, the subject would be eligible. The specimen will be evaluated at a central laboratory for expression status of PD-L1. Only subjects with PD-L1 positive tumors will be enrolled in the trial. PD-L1 predicting potential response to anti-PD-1 therapy is based on the results from Topalian et al [28] who examined PD-L1 expression in the archival specimens of 42 of the 296 subjects treated with the PD-1 inhibitor nivolumab. Of those 17 subjects whose tumor cells did not stain positive for PD-L1 using a 5% threshold of tumor cell surface expression, no objective response by RECIST 1.1 was observed. But among the 25 subjects whose tumor cells were considered positive for PD-L1, 9 responded (36%). Therefore, it is hypothesized that PD-L1 expression may be a predictive biomarker of anti-PD-1 activity, and this selection criterion will be utilized in this study as a necessary element for study enrollment.

4.2.2 Rationale for Dose Selection/Regimen/Modification

An open-label Phase I trial (KEYNOTE-001) is being conducted to evaluate the safety and clinical activity of single agent pembrolizumab. The dose escalation portion of this trial evaluated 3 dose levels, 1 mg/kg, 3 mg/kg, and 10 mg/kg, administered once every 2 weeks (Q2W) in subjects with advanced solid tumors. All 3 dose levels were well tolerated and no dose-limiting toxicities were observed. This first in human study of pembrolizumab showed evidence of target engagement and objective evidence of tumor size reduction at all dose levels (1 mg/kg, 3 mg/kg and 10 mg/kg Q2W). No maximum tolerated dose (MTD) has been identified to date. 10 mg/kg Q2W, the highest dose tested in KEYNOTE-001, will be the dose and schedule utilized in this protocol.

Pharmacokinetic (PK) data analysis of pembrolizumab administered Q2W showed slow systemic clearance, limited volume of distribution, and a long half-life (refer to Investigator's Brochure). Pharmacodynamic data (interleukin-2 release assay) suggested that peripheral target engagement is durable (>21 days). This early PK and pharmacodynamic data provide scientific rationale for testing a once every 3 weeks (Q3W) or more frequent dosing schedule.

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 PD-L1 positive advanced solid tumors. Response rates per RECIST 1.1 will be evaluated.

RECIST 1.1 [29] as assessed by the investigator will be used as the primary response rate efficacy endpoint. RECIST 1.1 will also be used by the local site to determine eligibility and make treatment decisions.

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 initial increase in tumor burden or even the appearance of new lesions. Standard RECIST may not provide an accurate response assessment of immunotherapeutic agents such as pembrolizumab. Therefore, RECIST 1.1 will be used with the following adaptations:

If radiologic imaging shows initial progressive disease (PD), tumor assessment should be repeated ≥4 weeks later in order to confirm PD with the option of continuing treatment per below while awaiting radiologic confirmation of progression. If repeat imaging shows a reduction in the tumor burden compared to the initial scan demonstrating PD, treatment may be continued / resumed. If repeat imaging confirms progressive disease, subjects will be discontinued from study therapy (exception noted in Section 7.1.2.5.1). In determining whether or not the tumor burden has increased or decreased, investigators should consider all target lesions as well as non-target lesions (please refer to the Procedure Manual).

In subjects who have initial evidence of radiological PD, it is at the discretion of the treating physician whether to continue a subject on study treatment until repeat imaging is obtained a minimum of 4 weeks later. This clinical judgment decision should be based on the subject's overall clinical condition, including performance status, clinical symptoms, and laboratory data. Subjects may receive pembrolizumab treatment while waiting for confirmation of PD if they are clinically stable as defined by the following criteria:

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

When feasible, subjects should not be discontinued until progression is confirmed. This allowance to continue treatment despite initial radiologic progression takes into account the

observation that some subjects can have a transient tumor flare in the first few months after the start of immunotherapy, but with subsequent disease response. Subjects that are deemed clinically unstable are not required to have repeat imaging for confirmation of progressive disease.

A retrospective central review may be performed for subjects using RECIST 1.1 criteria to assess best overall response. Response activity by RECIST 1.1 in GBM subjects may be retrospectively confirmed using central review RANO criteria [30], and similarly prostate cancer subject radiologic activity may be retrospectively confirmed using central PCWG2 criteria [31].

4.2.3.2 Safety Endpoints

The secondary safety objective of this study is to characterize the safety and tolerability of pembrolizumab in subjects with PD-L1 positive advanced solid tumors. The safety analysis will be based on subjects who experienced toxicities as defined by CTCAE criteria. Safety will be assessed by quantifying the toxicities and grades experienced by subjects who have received pembrolizumab, including 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 ECIs (irECI) as described in Section 7.2.3.2.

4.2.3.3 Biomarker Research

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

Assays may include, but are not limited to:

Transcriptional Analyses of Gene Expression Signatures

Objective: To assess the association between anti-tumor activity from pembrolizumab with several gene expression signatures related to PD-1/PD-L1 signaling

Messenger ribonucleic nucleic acid (mRNA) transcript profiling will be performed to assess gene expression and to evaluate specific gene sets that may correlate with clinical response to pembrolizumab.

Genetic Analysis

Objective: To assess the association between anti-tumor activity from genetic alterations that may indicate a specific genotype reflective of greater dependency on PD-1/PD-L1 checkpoint function or other immune checkpoint signaling pathways.

Deoxyribonucleic acid (DNA) isolated from blood or tumor tissue will be analyzed in order to identify genetic alterations and to evaluate specific genetic alterations that may correlate with clinical response to pembrolizumab. These and other additional biomarker or genomic research to identify factors important for pembrolizumab therapy (for example, human leukocyte antigen genotype) may also be pursued.

Multiparametric (2-Color) IHC

Spatial association of PD-1+ TILs and PD-L1+ cells (tumor and myeloid cells) suggests "induction" of PD-L1. By assessing both of the required elements, i.e. PD-L1 positive cells and PD-1+ T cells, a 2-color IHC assay may be a better predictor of response than PD-L1 positivity alone. These and other additional biomarker analyses may also be pursued to identify factors important for pembrolizumab therapy.

Additional exploratory analyses may be done when possible on available tumor specimens to evaluate other immune related checkpoints, genes, and cytokines, and their relationship to clinical responses to pembrolizumab therapy.

4.2.3.4 Future Biomedical Research

The Sponsor will conduct Future Biomedical Research on blood and tumor tissue specimens collected during this clinical trial. This research may include genetic analyses (DNA), gene expression profiling (ribonucleic acid [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.

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

Male/Female subjects with a PD-L1 positive advanced solid tumor (as prespecified in Section 2.1) of at least 18 years will be enrolled in this trial.

5.1.2 Subject Inclusion Criteria

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

1. Be willing and able to provide written informed consent/assent for the trial. The subject may also provide consent/assent for Future Biomedical Research. However, the subject may participate in the main trial without participating in Future Biomedical Research.
2. Be ≥18 years of age on the day of signing informed consent.
3. Have histologically or cytologically-documented, locally-advanced, or metastatic solid malignancy that is incurable and has either (a) failed prior standard therapy, (b) for which no standard therapy exists, or (c) standard therapy is not considered appropriate by the subject and treating physician. There is no limit to the number of prior treatment regimens.
4. Have one of the following advanced (unresectable and/or metastatic) solid tumor indications:

   A1 Colon or Rectal Adenocarcinoma
   A2 Anal Canal Squamous Cell Carcinoma
   A3 Pancreas Adenocarcinoma
   A4 Esophageal Squamous Cell Carcinoma or Adenocarcinoma (Including GE Junction)
   A5 Biliary Tract Adenocarcinoma (Gallbladder and Biliary Tree but excluding Ampulla of Vater Cancers)
   A6 Carcinoid Tumors
   A7 Neuroendocrine Carcinomas (Well or moderately differentiated Pancreatic Neuroendocrine Tumor)

   B1 ER Positive HER2 Negative Breast Cancer [a, d]
   B2 Ovarian Epithelial, Fallopian Tube or Primary Peritoneal Carcinoma
   B3 Endometrial Carcinoma [b]
   B4 Cervical Squamous Cell Cancer
   B5 Vulvar Squamous Cell Carcinoma

   C1 Small Cell Lung Cancer
   C2 Mesothelioma (Malignant Pleural Mesothelioma)

D1 Thyroid Cancer (Papillary or Follicular Subtype)
D2 Salivary Gland Carcinoma [b]
D3 Nasopharyngeal Carcinoma

E1 Glioblastoma Multiforme [c]
E2 Leiomyosarcoma
E3 Prostate Adenocarcinoma [d]

[a] *Note: ER positive HER2 negative status for breast cancer cohort defined by local standards.*
[b] *Note: All carcinoma subtypes are allowed however sarcomas or mesenchymal tumors are excluded.*
[c] *Note: Glioblastoma multiforme subjects with any prior bevacizumab treatment are NOT eligible (exceptions may be considered after consultation with the sponsor).*
[d] *Note: Subjects with prostate cancer who are currently on luteinizing-hormone-releasing hormone (LHRH) analogs and breast cancer subjects receiving LHRH analogs for ovarian suppression to avoid menses are eligible for this study and may continue to take the LHRH analogs while participating in this study.*

5. Have provided tissue for biomarker analysis from an archival tissue sample or newly obtained core or excisional biopsy of a tumor lesion not previously irradiated (tumors progressing in a prior site of radiation are allowed for PD-L1 characterization, other exceptions may be considered after Sponsor consultation).

6. Have a PD-L1 positive tumor as determined by IHC at a central laboratory from either an archived formalin-fixed, paraffin embedded (FFPE) tumor sample or a newly obtained biopsy.

7. Have measurable disease based on RECIST 1.1. Tumor lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions.

8. Have a performance status of 0 or 1 on the ECOG Performance Scale.

9. Demonstrate adequate organ function as defined in Table 1, all screening labs should be performed within 10 days of treatment initiation.

Table 1 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1,500 /mcL
Platelets	≥100,000 / mcL
Hemoglobin	≥9 g/dL or ≥5.6 mmol/L
Renal	
Creatinine **OR** Measured or calculated[a] creatinine clearance (GFR can also be used in place of creatinine or CrCl[a])	≤1.5xULN **OR** ≥60 mL/min for subject with creatinine levels >1.5x institutional ULN
Hepatic	
Total bilirubin	≤1.5xULN **OR** Direct bilirubin ≤ULN for subjects with total bilirubin levels >1.5xULN
AST (SGOT) and ALT (SGPT)	≤2.5xULN **OR** ≤5xULN for subjects with liver metastases
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT)	≤1.5xULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
Activated Partial Thromboplastin Time (aPTT)	≤1.5xULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
[a] Creatinine clearance (CrCl) should be calculated per institutional standard. ALT (SGPT)=alanine aminotransferase (serum glutamic pyruvic transaminase); AST (SGOT)=aspartate aminotransferase (serum glutamic oxaloacetic transaminase); GFR=glomerular filtration rate; ULN=upper limit of normal.	

10. Female subject 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.

11. Female subjects of childbearing potential must be willing to use an adequate method of contraception as outlined in Section 5.7.2 - Contraception, for the course of the trial through 120 days after the last dose of trial drug.

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

12. Male subjects of childbearing potential must agree to use an adequate method of contraception as outlined in Section 5.7.2 – Contraception starting with the first dose of study therapy through 120 days after the last dose of study therapy.

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

5.1.3 Subject Exclusion Criteria

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

1. Is currently participating and receiving study therapy or has participated in a study of an investigational agent and received study therapy or used an investigation device within 4 weeks of the first dose of treatment.

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

   Note: Systemic steroid therapy allowed for subjects in the GBM cohort as long as ≤ dexamethasone 4 mg, or its steroid equivalent (other exceptions may be considered after sponsor consultation).

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

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

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

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

   Note: Subjects in the GBM cohort are not eligible if they have had radiation therapy to their only sites of measurable central nervous system (CNS) disease within 12 weeks prior to study Day 1.

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

6. Has known active CNS metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least 4 weeks prior to the first dose of trial treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to trial treatment. This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability.

7. Has an 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.

8. Has evidence of interstitial lung disease or a history of (non-infectious) pneumonitis that required steroids or has current pneumonitis.

9. Has an active infection requiring systemic therapy.

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

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

12. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the pre-screening or screening visit through 120 days after the last dose of trial treatment.

13. Has previously participated in any other pembrolizumab trial, or received prior therapy with an anti-PD-1, anti-PD-L1, and anti-PD-L2 (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways).

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

15. Has known active Hepatitis B (e.g., hepatitis B surface antigen [HBsAg] reactive) or Hepatitis C virus (e.g., HCV RNA [qualitative] is detected).

16. Has received a live vaccine within 30 days of planned start of study therapy. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, Bacillus Calmette–Guérin (BCG), and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g., FluMist®) are live attenuated vaccines and are not allowed.

17. Is or has an immediate family member (spouse or children) 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.

5.2 Trial Treatment(s)

The study drug dose and schedule to be used in this trial are outlined below in Table 2.

Table 2 Trial Treatment

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/ Treatment Period	Use
Pembrolizumab	10 mg/kg	Q2W	IV infusion	Day 1 of each cycle	Experimental
The pembrolizumab dosing interval may be withheld due to toxicity as described in Section 5.2.1.2.					

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

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

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

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 and Rationale.

The dose amount required to prepare the pembrolizumab infusion solution will be based on the subject's weight in kilograms (kg). Details on the dose calculation, preparation and administration are provided in the Pharmacy Manual.

5.2.1.2 Dose Modification and Toxicity Management Guidelines for Pembrolizumab

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

Adverse events associated with pembrolizumab exposure may represent an immunologic etiology. These irAEs may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than on 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, skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab and administer corticosteroids. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab are provided in Table 3; additional guidance is provided Section 5.6.1.

For subjects whose dose was withheld due to toxicity, subjects may resume pembrolizumab upon resolution of toxicity to Grade 0-1 or baseline. This dose would be considered Day 1 of the next cycle and should be in alignment with the new schedule.

Table 3 Dose Modification and Toxicity Management Guidelines for Immune-related AEs Associated with Pembrolizumab

General instructions:

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

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

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

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

a. For subjects with liver metastasis who begin treatment with Grade 2 AST or ALT, if AST or ALT increases by greater than or equal to 50% relative to baseline and lasts for at least 1 week then subjects should be discontinued.

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

NOTE:

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

Dose modification and toxicity management of infusion-reactions related to pembrolizumab

Pembrolizumab may cause severe or life threatening infusion-reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab associated infusion reaction are provided in Section 5.6.1 (Table 5).

Other allowed dose interruption for pembrolizumab

Pembrolizumab may be interrupted for situations other than treatment-related AEs such as medical / surgical events or logistical reasons not related to trial therapy (e.g., elective surgery, unrelated medical events, subject vacation, and/or holidays). Subjects should be placed back on trial therapy within 12 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the subject's trial record.

5.2.2 Timing of Dose Administration

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

All study drug will be administered on an outpatient basis.

Pembrolizumab will be administered as a 30 minute IV infusion every 2 weeks (treatment cycle intervals may be withheld due to toxicity as described in Section 5.2.1.2). Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min).

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

Continuing Study Drug Administration After Initial Evidence of Radiologic Disease Progression

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 as a clinical response after an initial increase in tumor burden or even the appearance of new lesions.

If initial radiologic imaging shows PD, tumor assessment should be repeated ≥4 weeks later in order to confirm PD with the option of continuing treatment per below while awaiting

radiologic confirmation of progression. If repeat imaging shows a reduction in the tumor burden compared to the initial scan demonstrating PD, treatment may be continued as per treatment calendar. If repeat imaging confirms progressive disease, subjects will be discontinued from study therapy (exception noted in Section 7.1.2.5.1). In determining whether or not the tumor burden has increased or decreased, Investigators should consider all target lesions as well as non-target lesions (please refer to the Procedures Manual).

When feasible, subjects should not be discontinued until progression is confirmed; however, the decision to continue study treatment after the 1st evidence of disease progression is at the Investigator's discretion based on the clinical status of the subject as described in Table 4 below. Subjects may receive study treatment while waiting for confirmation of PD if they are clinically stable as defined by the following criteria:

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

Table 4 Imaging and Treatment After First Radiologic Evidence of Progressive Disease

	Clinically Stable		Clinically Unstable	
	Imaging	Treatment	Imaging	Treatment
1st radiologic evidence of PD	Repeat imaging at ≥4 weeks to confirm PD	May continue study treatment at the Investigator's discretion while awaiting confirmatory scan	Repeat imaging at ≥4 weeks to confirm PD if possible	Discontinue treatment
Repeat scan confirms PD	No additional imaging required	Discontinue treatment (exception noted in Section 7.1.2.5.1)	No additional imaging required	N/A
Repeat scan shows SD, PR or CR	Continue regularly scheduled imaging assessments every 8 weeks (after 6 months, imaging assessments every 12 weeks)	Continue study treatment at the Investigator's discretion	Continue regularly scheduled imaging assessments every 8 weeks (after 6 months, imaging assessments every 12 weeks)	May restart study treatment if condition has improved and/or clinically stable per Investigator's discretion

CR=completed response; N/A=not applicable; SD=stable disease; PD=progressive disease; PR=partial response

5.2.3 Trial Blinding/Masking

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

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 after 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 Medications

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

- Anti-cancer systemic chemotherapy or biological therapy

  Note: Subjects with glioblastoma multiforme with any prior bevacizumab treatment are not eligible (exceptions may be considered after consultation with the sponsor).

  Note: Subjects with prostate cancer who are currently on LHRH analogs and subjects with breast cancer receiving LHRH analogs for ovarian suppression to avoid menses are eligible for this study and may continue to take the LHRH analogs while participating in this study.

- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab
- Radiation therapy

  Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed after consultation with Sponsor.
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however intranasal influenza vaccines (e.g. Flu-Mist®) are live attenuated vaccines, and are not allowed
- Glucocorticoids for any purpose other than to modulate symptoms from an adverse event.

  Note: The use of physiologic doses (e.g., prednisone 10 mg) of corticosteroids may be approved after consultation with the Sponsor. Concomitant administration of higher steroid doses with study medication is prohibited.

  Note: Systemic steroid therapy allowed for subjects in the GBM cohort as long as ≤ dexamethasone 4 mg, or its steroid equivalent (other exceptions may be considered after sponsor consultation).

  Note: Use of prophylactic corticosteroids to avoid allergic reactions (e.g. IV contrast dye) 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.

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

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator including but not limited to the items outlined below:

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

symptomatic subjects, infectious etiologies should be ruled out, and if symptoms are persistent and/or severe, endoscopic evaluation should be considered.

  - All subjects who experience diarrhea 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.

- Nausea/vomiting: Nausea and vomiting should be treated aggressively, and consideration should be given in subsequent cycles to the administration of prophylactic antiemetic therapy according to standard institutional practice. Subjects should be strongly encouraged to maintain liberal oral fluid intake.

- Anti-infectives: Subjects with a documented infectious complication should receive oral or IV antibiotics or other anti-infective agents as considered appropriate by the treating investigator for a given infectious condition, according to standard institutional practice.

- Immune-related adverse events: Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined along with dose modification guidelines in Section 5.2.1.2, Table 3 and Section 5.6.1.1 below.

- Management of Infusion Reactions: Pembrolizumab may cause severe or life threatening infusion-reactions. Acute infusion reactions (which can include cytokine release syndrome, angioedema, or anaphylaxis) are different from allergic/hypersensitive reactions, although some of the manifestations are common to both AEs. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Signs/symptoms may include: Allergic reaction/hypersensitivity (including drug fever); Arthralgia (joint pain); Bronchospasm; Cough; Dizziness; Dyspnea (shortness of breath); Fatigue (asthenia, lethargy, malaise); Headache; Hypertension; Hypotension; Myalgia (muscle pain); Nausea; Pruritus/itching; Rash/desquamation; Rigors/chills; Sweating (diaphoresis); Tachycardia; Tumor pain (onset or exacerbation of tumor pain due to treatment); Urticaria (hives, welts, wheals); Vomiting. 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 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 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. **Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.**	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab with: Diphenhydramine 50 mg PO (or equivalent dose of antihistamine) Acetaminophen 500-1000 mg PO (or equivalent dose of analgesic)
Grades 3 or 4 Grade 3: Prolonged (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 • Epinephrine Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **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 drug administration. For Further information, please refer to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE) at http://ctep.cancer.gov IV=intravenous; NSAIDs= non-steroidal anti-inflammatory drugs; PO=oral administration		

The treatment guidelines are intended to be applied when the Investigator determines the events to be related to pembrolizumab.

Note: If after the evaluation of the event, it is determined not to be related to pembrolizumab, the Investigator does not need to follow the treatment guidance. Refer to Section 5.2.1.2, Table 3 for guidelines regarding dose modification and supportive care.

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

5.6.1.1 Supportive Care Guidelines for Events of Clinical Interest and Immune-related Adverse Events (irAEs)

Immune-related Adverse Events (irAE)

Adverse events (both non-serious and serious) associated with drug exposure and consistent with an immune phenomenon may represent an immunologic etiology. These irAEs may be predicted based on the nature of the pembrolizumab compound, its mechanism of action, and reported experience with immunotherapies that have a similar mechanism of action. An irAE can occur shortly after the first dose or several months after the last dose of treatment and may affect more than on body system simultaneously. Particular attention should be paid to AEs that may be suggestive of potential irAEs as outlined in 7.2.3.2. 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. 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 Section 5.2.1.2, Table 3.

Events of Clinical Interest (ECI)

Events of clinical interest (ECI) are non-serious and serious adverse events that may or may not be irAEs. ECIs must be reported to Merck **within 24 hours** regardless of attribution to study treatment. Information on how to identify and report ECIs can be referenced in Section 7.2.3.2.

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 MK 3475 has transient adverse effects on the composition of sperm.

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

Female subjects will be considered of non-reproductive potential if they meet 1 of the following criteria:

- She is postmenopausal, defined as at least 12 months with no menses without an alternative medical cause. In women <45 years of age who are not using hormonal contraception or hormonal replacement therapy, a high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state. In the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
- She had a hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy or bilateral tubal ligation/occlusion, at least 6 weeks prior to screening.
- She has a congenital or an acquired condition that prevents childbearing.

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

- Practice abstinence from heterosexual activity.

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

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

Acceptable methods of contraception are‡:

- Single method (1 of the following is acceptable):
  - Intrauterine device (IUD)
  - Vasectomy of a female subject's male partner
  - Contraceptive rod implanted into the skin
- Combination method (requires use of 2 of the following):
  - Diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide)
  - Cervical cap with spermicide (nulliparous women only)
  - Contraceptive sponge (nulliparous women only)

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

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

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

5.7.3 Use in Pregnancy

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

5.7.4 Use in Nursing Women

It is unknown whether pembrolizumab is excreted in human milk. 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.

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.

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.

5.8.1 Discontinuation of Treatment

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 outlined in Section 7.1.2.5.1 (exception if the Sponsor approves treatment continuation).

  Note: For unconfirmed radiographic disease progression, please see Section 5.2.2

  Note: A subject may be granted an exception to continue on treatment with confirmed radiographic progression if clinically stable or clinically improved, please see Section 7.1.2.5.1
- Unacceptable adverse experiences as described in Section 5.2.1.2 and Section 7.2
- Any progression or recurrence of any malignancy, or any occurrence of another malignancy that requires active treatment
- Intercurrent illness other than another malignancy as noted above that prevents further administration of treatment
- Investigator's decision to withdraw the subject
- A confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements
- Recurrent Grade 2 pneumonitis
- The subject is lost to follow-up
- Completed 24 months of treatment with pembrolizumab

  Note: 24 months of study medication is calculated from the date of first dose. Subjects who stop pembrolizumab after 24 months may be eligible for up to 1 year of additional study treatment if they progress after stopping study treatment provided they meet the requirements detailed in Section 7.1.5.2.1.

- Discontinuation of treatment may be considered for subjects who have attained a confirmed CR that have been treated for at least at least 24 weeks, receiving at least 2 doses of pembrolizumab beyond the date when the initial CR was declared. Subjects who stop pembrolizumab with SD, PR, or CR, may be eligible for up to 1 year of pembrolizumab if they experience disease progression after stopping pembrolizumab. This retreatment is termed the Second Course Phase (Retreatment) and is described in detail in Section 7.1.5.2.1.

- Administrative reasons

The End of Treatment and Follow-up visit procedures are listed in Section 6.0 (Protocol Flow Chart) and Section 7.1.5 (Visit Requirements). After the end of treatment, each subject will be followed for 30 days for AE monitoring (serious adverse events will be collected for 90 days after the end of treatment 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 OS until death, withdrawal of consent, or the end of the study, whichever occurs first.

5.9 Subject Replacement Strategy

Additional subjects may be enrolled in a given cohort to ensure that the required number of evaluable subjects in each cohort is achieved. A subject that discontinues the trial for progressive disease or a drug-related AE will not be replaced and will be counted in the evaluable population of subjects for the respective cohort. Further details are provided in Section 8.1.3.

5.10 Beginning and End of the Trial

The study begins when the first subject signs the informed consent (either pre-screening consent or main study consent). The end of the study may be designated as the time point when all subjects have discontinued the study or are a minimum of 6 months post initial study medication administration. If, by the end of the study, there remains at least 1 subject still on study treatment for at least 6 months, the subject(s) may enter additional treatment cycles. At this point a database lock of the trial may occur to allow the analysis of the study data. Any remaining subjects may continue to receive study medication and be seen by the investigator per usual standard of care for this subject population. In addition, the investigator will be expected to monitor for and report any serious adverse events, events of clinical interest, and pregnancies, as detailed in Section 7.2.3 (Serious Adverse Experiences). The subject is considered on study until such time that he/she meets any of the discontinuation criteria and written notification is given to the Sponsor.

Upon study completion, subjects are discontinued and enrolled in a pembrolizumab extension study.

5.11 Clinical Criteria for Early Trial Termination

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

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

6.0 TRIAL FLOW CHART

6.1 Study Flow Chart

Trial Period:	**Screening Phase**	**Treatment Cycles [a]**								**End of Treatment**	**Post-Treatment**		
						To be repeated beyond 8 cycles [a]							
Treatment Cycle/Title:	Screening (Visit 1)	1	2	3	4	5	6	7	8	Discon	Safety Follow-up	Follow Up Visits [b]	Survival Follow-Up
Scheduling Window (Days):	-28 to -1		± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days from last dose (± 3 days)	Every 12 weeks post discon (± 7 days)	Every 12 weeks (± 4 weeks)
Administrative Procedures													
Pre-screening Consent	X [c]												
Informed Consent	X [d]												
Informed Consent for Future Biomedical Research (optional)	X												
Inclusion/Exclusion Criteria	X												
Subject Identification Card	X												
Demographics and Medical History	X												
Prior and Concomitant Medication Review	X [f]	X	X	X	X	X	X	X	X	X	X [f]		
Trial Treatment Administration		X	X	X	X	X	X	X	X				
Post-study Anticancer Therapy Status												X	X
Survival Status [w]		←----------										----------→	X
Clinical Procedures/Assessments													
Review Adverse Events	X	X	X	X	X	X	X	X	X	X	X [g]	X [g]	
Full Physical Examination	X					X [h]							
Directed Physical Examination		X	X	X	X		X [u]	X [u]	X [u]	X			
Vital Signs and Weight [i]	X	X	X	X	X	X	X	X	X	X			
ECOG Performance Status	X	X	X	X	X	X	X [v]	X [v]	X [v]	X			

Trial Period:	**Screening Phase**	**Treatment Cycles [a]**								**End of Treatment**	**Post-Treatment**		
						To be repeated beyond 8 cycles [a]							
Treatment Cycle/Title:	Screening (Visit 1)	1	2	3	4	5	6	7	8	Discon	Safety Follow-up	Follow Up Visits [b]	Survival Follow-Up
Scheduling Window (Days):	-28 to -1		± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days from last dose (± 3 days)	Every 12 weeks post discon (± 7 days)	Every 12 weeks (± 4 weeks)
Laboratory Procedures/Assessments: analysis performed by LOCAL laboratory													
Pregnancy Test – Urine or Serum β-human chorionic gonadotropin (β-HCG) [k]	X												
PT/INR and aPTT	X [l]												
CBC with Differential [m]	X [l]		X	X	X	X	X	X	X	X	X [n]		
Comprehensive Chemistry Panel [m]	X [l]		X	X	X	X	X	X	X	X	X [n]		
Urinalysis [m]	X [l]					X [h]					X [n]		
Total triiodothyronine (T3), free thyroxine (FT4) and thyroid stimulating hormone (TSH) [m]	X [l]					X [h]					X [n]		
Tumor Marker Assessment (Optional) [j]	X [j]					X [j]				X [j]		X [j]	
Laboratory Procedures/Assessments: analysis performed by CENTRAL laboratory													
Blood for Future Biomedical Research [o]		X											
Efficacy Measurements													
Tumor Imaging [a,p,q]	X					X				X [r]		X [b]	
Tumor Biopsies/Archival Tissue Collection/Correlative Studies Blood													
Archival or Newly Obtained Tissue Collection [e]	X [s]												
Correlative Studies Blood Collection [e]		X [t]				X [t]				X [t]			

a. Treatment cycles are 2 weeks. Imaging should be performed every 8 weeks initially (56 days ± 7 days) and after 6 months, imaging assessments should be performed every 12 weeks regardless of any treatment delays (i.e. Screening visit, Cycle 5, Cycle 9, Cycle 13 and then every 6 cycles (12 weeks)).
b. In subjects who discontinue study therapy without documented disease progression, every effort should be made to continue monitoring their disease status by radiologic imaging[p] every 8 weeks (± 7 days) in the first 6 months and every 12 weeks (± 7 days) after Month 6 until (1) the start of new anti-cancer treatment, (2) documented disease progression, (3) death, or (4) the end of the study, whichever occurs first.
c. Pre-screening informed consent must be obtained prior to sending an archival sample to the vendor for characterization. Subjects that do not have archival tissue available must sign the main study consent prior to undergoing a newly obtained biopsy.
d. Written consent must be obtained prior to performing any protocol specific procedure. Results of a test performed prior to the subject signing consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame (e.g., within 28 days prior to the first dose of trial treatment). Baseline number will be assigned when the study informed consent is signed.
e. Leftover samples may be kept for Future Biomedical Research if the subject signs the Future Biomedical Research (FBR) consent.
f. Prior medications – Record all medications taken 28 days before the first dose of trial treatment. Concomitant medications – Enter new medications started during the trial and 30 days after last dose of trial treatment regardless of when the Safety Follow-up visit occurs.
g. Record all AEs occurring within 30 days after the last dose of trial treatment regardless of when the Safety Follow-up visit occurs. After 30 days, record all SAEs (related and unrelated to trial treatment) / ECIs occurring up to 90 days after the last dose of trial treatment or the start of new anti-cancer treatment, whichever comes first. Afterwards, any drug related AE regardless of seriousness occurring outside of any reporting timeframes must be reported
h. To be repeated every 4 cycles after Cycle 5.
i. Height will be measured at visit 1 only.
j. Tumor marker assessment is not an additional study-related laboratory evaluation. The purpose is to collect information that may be a part of standard clinical assessment for certain tumor types. Data collection (if applicable and if available) should occur every 8 weeks initially (56 days ± 7 days) and after 6 months, assessments should be performed every 12 weeks regardless of any treatment delays (i.e. Screening visit, Cycle 5, Cycle 9, Cycle 13 and then every 6 cycles (12 weeks) thereafter coinciding with imaging visits). Upon discontinuation, tumor marker data collection will occur at the same time as post-treatment imaging follow-up visits. See Section 7.1.2.7 and Section 7.1.3.1 for additional details.
k. For women of reproductive potential, a urine pregnancy test should be performed within 72 hours prior to first dose of trial treatment. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test performed by the local study site laboratory will be required. Pregnancy tests (serum and/or urine tests) should be repeated if required by local guidelines.
l. Laboratory tests for screening are to be performed within 10 days prior to the first dose of trial treatment. See Section 7.1.3 for details regarding laboratory tests.
m. After Cycle 1, lab samples can be collected up to 72 hours prior to the scheduled time point. See Section 7.1.3 for details regarding laboratory tests.
n. Unresolved abnormal labs that are drug related AEs should be followed until resolution.
o. Informed consent for future biomedical research samples must be obtained before the DNA sample. 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.
p. The initial tumor imaging will be performed within 28 days prior to the first dose of trial treatment. Scans performed as part of routine clinical management are acceptable for use as the screening scan if they are of diagnostic quality and performed within 28 days prior to the first dose of trial treatment. On-study imaging will be performed every 8 weeks (± 7 days) after the first dose of trial treatment (after 6 months, imaging assessments every 12 weeks) and should follow calendar days and should not be adjusted for delays in cycle starts or withholding of pembrolizumab cycle frequencies. The same imaging technique should be used in a subject throughout the trial. Local reading (investigator assessment with site radiology reading) will be used to determine eligibility and for subject management. Tumor imaging and assessment per local standard of care should be performed for subject management, and may include

additional imaging (e.g. bone scan for subjects with prostate cancer) and appropriate tumor markers. Sponsor will collect radiological assessments for retrospective analysis by a central vendor. The processes for image collection and transmission to the central vendor are in the Site Imaging Manual (SIM).

q. Per the modified RECIST 1.1 used in this protocol, if imaging shows progressive disease, the imaging assessment should be repeated at a minimum of 4 weeks later in order to confirm progressive disease as described in Section 4.2.3.1.
r. If a scan was obtained within 4 weeks prior to the date of discontinuation, then a scan at treatment discontinuation isn't mandatory. In subjects who discontinue study therapy without confirmed disease progression, a radiological evaluation should be repeated at the time of treatment discontinuation (i.e. date of discontinuation ± 4 week window).
s. Baseline tumor tissue for biomarker analysis from an archival tissue sample or newly obtained core or excisional biopsy (fine needle aspiration [FNA] not adequate) of a tumor lesion not previously irradiated must be provided (tumors progressing in a prior site of radiation are allowed for PD-L1 characterization, other exceptions may be considered after Sponsor consultation) and received by the central vendor for characterization of PD-L1 status prior to enrollment. These samples are not required to be obtained within 28 days of enrollment.
t. Blood for correlative studies should be collected prior to Cycle 1, at Cycle 5 and again at discontinuation (end of treatment).
u. Directed physical exams are performed at Cycles 1, 2, 3, 4, 6, 7, 8 and 11. After Cycle 11, directed physical exams should occur once every 4 cycles (Cycles 15, 19, etc.).
v. Following Cycle 8, the ECOG performance status should be determined only in conjunction with a protocol-specified full or directed physical exam (Cycle 9, 11, 13, 15, 17, 19 and every 2 cycles thereafter.
w. After documented local site assessed disease progression or the start of new anticancer treatment; continuing subjects will be contacted approximately every 12 weeks by telephone. Updated survival status may be requested by the Sponsor at any time during the course of the study. Upon Sponsor notification, all subjects who do not/will not have a scheduled study visit or study contact during the Sponsor defined time period will be contacted for their survival status (excluding subjects that have a death event previously recorded).

6.2 Second Course Phase (Retreatment ONLY)

Trial Period:	SECOND COURSE PHASE: Treatment Cycles [a]								End of Treatment	Post-Treatment		
					To be repeated beyond 8 cycles [a]							
Treatment Cycle/Title:	1	2	3	4	5	6	7	8	Discon	Safety Follow-up	Follow Up Visits [b]	Survival Follow-Up
Scheduling Window (Days):		± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of discon	30 days from last dose (± 3 days)	Every 12weeks post discon (± 7 days)	Every 12 weeks (± 4 weeks)
Administrative Procedures												
Eligibility Criteria [c]	X											
Concomitant Medication Review [d]	X	X	X	X	X	X	X	X	X	X		
Trial Treatment Administration [e]	X	X	X	X	X	X	X	X				
Post-study Anticancer Therapy Status											X	X
Survival Status[r]	←----------										----------→	X
Clinical Procedures/Assessments												
Review Adverse Events	X	X	X	X	X	X	X	X	X	X [f]	X [f]	
Full Physical Examination	X				X [g]							
Directed Physical Examination		X	X	X		X [o]	X [o]	X [o]	X			
Vital Signs and Weight	X	X	X	X	X	X	X	X	X			
ECOG Performance Status	X	X	X	X	X	X [p]	X [p]	X [p]	X			
Laboratory Procedures/Assessments: analysis performed by LOCAL laboratory												
Pregnancy Test – Urine or Serum β-HCG [h]	X											
PT/INR and aPTT	X [i]											
CBC with Differential [j]	X [i]	X	X	X	X	X	X	X	X	X [n]		
Comprehensive Chemistry Panel [j]	X [i]	X	X	X	X	X	X	X	X	X [n]		
T3, FT4 and TSH [j]	X [i]				X [g]					X [n]		
Tumor Marker Assessment (Optional) [q]	X				X				X		X	
Efficacy Measurements												
Tumor Imaging [a,k,l]	X				X				X [m]		X [b]	

a. Treatment cycles are 2 weeks. Imaging should be performed every 8 weeks initially (56 days ± 7 days) and after 6 months, imaging assessments should be performed every 12 weeks regardless of any treatment delays (i.e. Screening visit, Cycle 5, Cycle 9, Cycle 13and then every 6 cycles (12 weeks)).
b. In subjects who discontinue study therapy without documented disease progression, every effort should be made to continue monitoring their disease status by radiologic imaging every 12 weeks (± 7 days) until (1) the start of new anti-cancer treatment, (2) documented disease progression, (3) death, or (4) the end of the study, whichever occurs first.
c. Subjects who either a) attain a CR and discontinue treatment or b) discontinue treatment after 24 months on pembrolizumab for reasons other than disease progression or intolerability may restart trial treatment if they meet the criteria specified in Section 7.1.5.2.1.
d. Concomitant medications – Enter new medications started during the trial and 30 days after last dose of trial treatment regardless of when the Safety Follow-up visit occurs.
e. Subjects who restart treatment should resume at the same dose and cycle interval which they were receiving prior to discontinuation.
f. Record all AEs occurring within 30 days after the last dose of trial treatment regardless of when the Safety Follow-up visit occurs. After 30 days record all SAEs (related and unrelated to trial treatment) / ECIs occurring up until 90 days after the last dose of trial treatment or the start of new anti-cancer treatment, whichever comes first. Afterwards, any drug related AE regardless of seriousness occurring outside of any reporting timeframes must be reported.
g. To be repeated every 4 cycles after Cycle 5.
h. For women of reproductive potential, a urine pregnancy test will be performed within 72 hours prior to first dose of retreatment. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test performed by the local study site laboratory will be required. Pregnancy tests (serum and/or urine tests) should be repeated if required by local guidelines.
i. Laboratory tests for determining eligibility for retreatment are to be performed within 10 days prior to the first retreatment dose of pembrolizumab. See Section 7.1.3 for details regarding laboratory tests.
j. After the first dose, lab samples can be collected up to 72 hours prior to the scheduled time point. See Section 7.1.3 for details regarding laboratory tests.
k. A scan must be performed within 28 days prior to restarting treatment with pembrolizumab. Imaging should continue to be performed every 12 weeks (84 ± 7 days) from the first dose of trial treatment or more frequently if clinically indicated. Imaging timing should follow calendar days and should not be adjusted for delays in cycle starts or withholding of pembrolizumab cycle frequencies. The same imaging technique should be used in a subject throughout the trial. Local reading (investigator assessment with site radiology reading) will be used to determine eligibility and for subject management. Tumor imaging and assessment per local standard of care should be performed for subject management, and may include additional imaging (e.g. bone scan for subjects with prostate cancer) and appropriate tumor markers. The Sponsor will collect radiological assessments for retrospective analysis by a central vendor. The processes for image collection and transmission to the central vendor are in the SIM.
l. Per the modified RECIST 1.1 used in this protocol, if imaging shows progressive disease, the imaging assessment should be performed at a minimum of 4 weeks later in order to confirm progressive disease as described in Section 4.2.3.1.
m. If a scan was obtained within 4 weeks prior to the date of discontinuation, then a scan at treatment discontinuation isn't mandatory. In subjects who discontinue study therapy without confirmed disease progression, a radiological evaluation should be performed at the time of treatment discontinuation (i.e. date of discontinuation ± 4 week window). If a previous scan was obtained within 4 weeks prior to the date of discontinuation, then a scan at treatment discontinuation isn't mandatory.
n. Unresolved labs that are drug related AEs should be followed until resolution.
o. Directed physical exams are performed at Cycles 2, 3, 4, 6, 7, 8 and 11. After Cycle 11, directed physical exams should occur once every 4 cycles (Cycles 15, 19, etc.).
p. Following Cycle 8, the ECOG performance status should be determined only in conjunction with a protocol-specified full or directed physical exam (Cycle 9, 11, 13, 15, 17, 19 and every 2 cycles thereafter.
q. Tumor marker assessment is not an additional study-related laboratory evaluation. The purpose is to collect information that may be a part of standard clinical assessment for certain tumor types. Data collection (if applicable and if available) should occur every 8 weeks initially (56 days ± 7 days) and after 6 months, assessments should be performed every 12 weeks regardless of any treatment delays (i.e. Screening visit, Cycle 5, Cycle 9, Cycle 13 and then every 6 cycles (12 weeks) thereafter coinciding with imaging visits). Upon discontinuation, tumor marker data collection will occur at the same time as post-treatment imaging follow-up visits. See Section 7.1.2.7 and Section 7.1.3.1 for additional details.
r. After documented local site assessed disease progression, or the start of new anticancer treatment; continuing subjects will be contacted approximately every 12 weeks by telephone. Updated survival status may be requested by the Sponsor at any time during the course of the study. Upon Sponsor notification, all subjects who do not/will not have a scheduled study visit or study contact during the Sponsor defined time period will be contacted for their survival status (excluding subjects that have a death event previously recorded).

7.0 TRIAL PROCEDURES

7.1 Trial Procedures

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

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

7.1.1 Administrative Procedures

7.1.1.1 Informed Consent

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

7.1.1.1.1 General Informed Consent

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

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

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

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

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

7.1.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

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

7.1.1.2 Inclusion/Exclusion Criteria

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

7.1.1.3 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.

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 disease for which the subject has enrolled in this study will be recorded separately and not listed as medical history.

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 starting the trial. Treatment for the disease for which the subject has enrolled in the study will be recorded separately and not listed as a prior medication.

7.1.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the subject during the trial through the Safety Follow-up visit. In addition, new medications started during the Second Course Phase through the Second Course Safety Follow-up visit should be recorded.

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

7.1.1.6 Disease Details and Treatments

7.1.1.6.1 Disease Details

The investigator or qualified designee will obtain prior and current details regarding disease status.

7.1.1.6.2 Prior Treatment Details

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

7.1.1.6.3 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.

7.1.1.7 Assignment of Screening Number

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

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

7.1.1.8 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. This unique number is termed a randomization number throughout the protocol for operational purposes. 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.

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

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

Administration of trial medication will be witnessed by the investigator and/or trial staff. The total volume of trial treatment infused will be compared to the total volume prepared to determine compliance with each dose administered.

The instructions for preparing and administering pembrolizumab will be provided in the Pharmacy Manual.

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 (Section 6.0) and more frequently if clinically indicated. Adverse events will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 4.0 (see Section 12.5). Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

All AEs of unknown etiology associated with pembrolizumab exposure should be evaluated to determine if it is possibly an ECI of a potentially immunologic etiology (irAE) (See Section 5.6.1.1).

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

7.1.2.2 Physical Exam

7.1.2.2.1 Full Physical Exam

The investigator or qualified designee will perform a complete physical exam during the screening period. Clinically significant abnormal findings should be recorded as medical history. A full physical exam should be performed during Screening, at Cycle 5 and every 4 cycles thereafter (Cycle 9, 13, 17, etc.) per the Trial Flow Chart (Section 6.0). 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 (Section 6.0), the investigator or qualified designee will perform a directed physical exam as clinically indicated prior to the administration of the trial treatment (Cycles 1, 2, 3, 4, 6, 7, 8 and 11). After Cycle 11 directed physical exams should occur once every 4 cycles thereafter (Cycles 15, 19, etc.). 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 (Section 6.0). Vital signs should include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at screening only.

7.1.2.4 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status (see Section 12.4) at screening, prior to the administration of each dose of trial treatment and discontinuation of trial treatment as specified in the Trial Flow Chart. After Cycle 8 assessment of ECOG status will be performed every other cycle in conjunction with the directed or full physical exam.

7.1.2.5 Tumor Imaging and Assessment of Disease

Processes for image collection and transmission to the central vendor can be found in the Site Imaging Manual (SIM). Tumor imaging is strongly preferred to be acquired by computed tomography (CT). Magnetic resonance imaging (MRI) should be used only when CT is contraindicated or for imaging of the brain. The same imaging technique regarding modality and the use of contrast should be used in a subject throughout the trial to optimize the visualization of existing and new tumor burden. Please refer to the SIM for guidance on imaging parameters, required anatomic regions and modality options.

7.1.2.5.1 Assessment of Disease

RECIST 1.1 will be applied by the site as the primary measure for assessment of tumor response and as a basis for all protocol guidelines related to disease status (e.g., discontinuation of study therapy).

RECIST 1.1 will be adapted as follows to account for the unique tumor response seen in this class of therapeutics.

If imaging shows PD, tumor assessment should be repeated ≥4 weeks later in order to confirm PD with the option of continuing treatment for clinically stable subjects as discussed below in Table 6.

Clinically stable is defined 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 (e.g., cord compression) requiring urgent alternative medical intervention

Table 6 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 to confirm PD	May continue study treatment at the Investigator's discretion while awaiting confirmatory scan	Repeat imaging at ≥ 4 weeks to confirm PD if possible	Discontinue treatment
Repeat scan confirms PD	No additional imaging required	Discontinue treatment (exception noted in Section 7.1.2.5.1)	No additional imaging required	N/A
Repeat scan shows SD, PR or CR	Continue regularly scheduled imaging assessments every 8 weeks (after 6 months every 12 weeks)	Continue study treatment at the Investigator's discretion	Continue regularly scheduled imaging assessments every 8 weeks (after 6 months every 12 weeks)	May restart study treatment if condition has improved and/or clinically stable per Investigator's discretion

CR=completed response; N/A=not applicable; SD=stable disease; PD=progressive disease; PR=partial response

In determining whether or not the tumor burden has increased or decreased, Investigators should consider all target lesions as well as non-target lesions (please refer to the Procedures Manual). Subjects that are deemed clinically unstable are not required to have repeat imaging for confirmation. If radiologic progression is confirmed, then the subject will be discontinued from trial treatment. If radiologic progression is not confirmed, then the subject should resume/continue trial treatment and have their next scan according to the every 8 or 12 weeks (56 or 84 ±7 days) schedule based on their on-treatment imaging frequency.

NOTE: If a subject with confirmed radiographic progression (i.e., 2 scans at least 28 days apart demonstrating progressive disease) is clinically stable or clinically improved, and there is no further increase in the tumor dimensions at the confirmatory scan, an exception may be considered to continue treatment upon consultation with the Sponsor. Clinically stable subjects should also have at the confirmatory scan no further increase in the target lesions, no unequivocal increase in non-target lesions, and no additional new lesions develop (non-worsening PD) to continue study treatment.

Subjects who discontinue trial treatment in the First Course Phase, for reasons other than disease progression, should continue tumor imaging using the same imaging schedule used while on treatment (every 8 weeks (±7 days) in the first 6 months, and every 12 weeks (±7 days) after Month 6) until the subject experiences confirmed disease progression or starts a new anti-cancer therapy. In the Second Course phase imagining assessments should be

performed every 12 weeks (±7 days) until the subject experiences confirmed disease progression or starts a new anti-cancer therapy.

Local reading (investigator assessment with site radiology reading) based on RECIST 1.1 will be used to determine subject eligibility and for subject management. Tumor imaging and assessment per local standard of care should be performed for subject management, and may include additional imaging (e.g. bone scan for subjects with prostate cancer) and appropriate tumor markers. The Sponsor will also receive radiologic images for a retrospective analysis of subject eligibility and treatment response to be performed by a central vendor, which may include RECIST 1.1, RANO, PCWG2 tumor response.

7.1.2.5.2 Initial Tumor Imaging

Initial tumor imaging at Screening must be performed within 28 days prior to the first dose of trial treatment. The site trial team must review screening images to confirm the subject has measurable disease per RECIST 1.1. The screening imaging scan must be submitted to the central imaging vendor for a possible retrospective analysis of this eligibility criterion.

Scans performed as part of routine clinical management are acceptable for use as the screening scan if they are of diagnostic quality and performed within 28 days prior to the first dose of trial treatment. The same imaging technique should be used in a subject throughout the study.

7.1.2.5.3 Tumor Imaging During Trial

Tumor imaging may be performed by CT or magnetic resonance imaging (MRI), but the same imaging technique should be used in a subject throughout the trial. Imaging should be performed every 8 weeks (56 days ± 7 days) from the first dose of trial treatment or more frequently if clinically indicated. After 6 months, imaging should be performed every 12 weeks (84 ± 7 days). Imaging timing should follow calendar days and should not be delayed for delays in cycle starts or withholding of pembrolizumab cycle intervals.

Per RECIST 1.1, PR and CR response should be confirmed by a repeat radiographic assessment not less than 4 weeks from the date the response was first documented. The tumor imaging performed for confirmation of response may be performed at the earliest 4 weeks after the first indication of response, or at the next scheduled scan, whichever is clinically indicated.

Imaging should continue to be performed until documented disease progression, the start of new anti-cancer treatment, withdrawal of consent, death, or the end of the study, whichever occurs first. Disease progression should be confirmed at least 4 weeks after the first scan indicating progressive disease in clinically stable subjects. Subjects who have unconfirmed disease progression may continue on treatment until progression is confirmed provided they have met the conditions detailed in Section 7.1.2.5.1.

7.1.2.5.4 End of Treatment and Follow-up Tumor Imaging

In subjects who discontinue trial treatment, tumor imaging should be performed at the time of treatment discontinuation (±4 week window). If a previous scan was obtained within 4 weeks prior to the date of discontinuation, then a scan at treatment discontinuation is not mandatory. In subjects who discontinue trial treatment due to documented disease progression, this is the final required tumor imaging.

In subjects who discontinue trial treatment without documented disease progression, every effort should be made to continue monitoring their disease status by tumor imaging using the same imaging schedule used while on treatment (every 8 weeks (±7 days) in the first 6 months, and every 12 weeks (±7 days) after Month 6) until the start of a new anticancer treatment, disease progression, death, or the end of the trial, whichever occurs first.

7.1.2.5.5 Second Course (Retreatment) Tumor Imaging

A scan must be performed within 28 days prior to restarting treatment with pembrolizumab. Local reading (Investigator assessment with site radiology reading) will be used to determine eligibility and subject management. Imaging should be submitted to the central imaging vendor for retrospective review.

The first on-trial imaging assessment should be performed at 12 weeks (84 days ±7 days) after the restart of treatment. Subsequent tumor imaging should be performed every 12 weeks (84 days ±7 days), or more frequently if clinically indicated.

Per the modified RECIST 1.1 used in this protocol (Section 7.1.2.5.1), if tumor imaging shows initial PD, tumor assessment should be repeated ≥4 weeks later in order to confirm PD with the option of continuing treatment while awaiting radiologic confirmation of progression. Subjects who obtain a confirmation scan do not need to undergo scheduled tumor imaging if it is 4 weeks later and may wait until the next scheduled imaging time point if clinically stable.

Imaging should continue to be performed until disease progression, the start of a new anticancer treatment, withdrawal of consent, death, or notification by the Sponsor, whichever occurs first. Disease progression may be confirmed at least 4 weeks after the first tumor imaging indicating PD in clinically stable subjects.

In subjects who discontinue trial treatment, tumor imaging should be performed at the time of treatment discontinuation (±4 week window). If a previous scan was obtained within 4 weeks prior to the date of discontinuation, then a scan at treatment discontinuation is not mandatory. In subjects who discontinue trial treatment due to documented disease progression, this is the final required tumor imaging.

In subjects who discontinue trial treatment without documented disease progression, every effort should be made to continue monitoring their disease status by radiologic imaging every 12 weeks (±7 days) until either the start of a new anticancer treatment, disease progression, death, or the end of the trial, whichever occurs first.

7.1.2.6 Tumor Tissue Collection and Correlative Studies Blood Sampling

Enrollment in this study is limited to those subjects with tumors that are characterized as PD-L1 positive by IHC. Archived FFPE tumor sample or newly obtained core or excisional biopsy (FNA not adequate) must be submitted for characterization at a central lab to determine subject eligibility. These samples are not required to be obtained within 28 days of enrollment, however, a biopsy for screening purposes cannot be performed until the main consent is signed.

Blood for correlative biomarker studies should be collected prior to Cycle 1, at Cycle 5 and upon Discontinuation / End of Treatment.

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

7.1.2.7 Tumor Marker Assessment (Optional)

Tumor marker assessment is not an additional study-related laboratory evaluation. The purpose is to collect information that may be a part of standard clinical assessment for certain tumor types. Data collection (if applicable and if available) should occur every 8 weeks (± 7 days) initially and after 6 months, assessments should be performed every 12 weeks (± 7 days) regardless of any treatment delays (i.e., Screening visit, Cycle 5, Cycle 9, Cycle 13 and then every 6 cycles [12 weeks] thereafter coinciding with imaging visits). Upon discontinuation, tumor marker data collection will occur at the same time as post-treatment imaging follow-up visits.

Table 7 shows tumor types that are commonly evaluated using markers.

Table 7 Tumor Markers and Associated Tumor Type

Tumor Type	Tumor Marker
ER Positive HER2 Negative Breast Cancer	Cancer Antigen 15-3 (CA 15-3)
	Cancer Antigen 27-29 (CA 27-29)
Carcinoid Tumors	Chromogranin A (CgA)
	5-Hydroxyindoleacetic acid (5-HIAA) (24 hours in urine)
Colon or Rectal Adenocarcinoma	Carcinoembryonic Antigen (CEA)
Neuroendocrine Carcinoma	Chromogranin A (CgA)
	5-Hydroxyindoleacetic acid (5-HIAA) (24 hours in urine)
Ovarian Epithelial, Fallopian Tube or Primary Peritoneal Carcinoma	Cancer Antigen 125 (CA-125)
Pancreas Adenocarcinoma	Carbohydrate Antigen 19-9 (CA 19-9)
Prostate Adenocarcinoma	Prostate-Specific Antigen (PSA)
Thyroid Cancer	Thyroglobulin (Tg)

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. Refer to the Trial Flow Chart (Section 6.0) for the timing of laboratory assessments.

7.1.3.1 Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

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

Table 8 Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Blood	Serum β-human Chorionic Gonadotropin [a]
Hemoglobin	Alkaline Phosphatase	Glucose	(β-hCG) [a]
Platelet Count	Alanine Aminotransferase (ALT)	Protein	PT (INR)
White Blood Cell (Total and Differential)	Aspartate Aminotransferase (AST)	Specific Gravity	aPTT
Red Blood Cell Count	Lactate Dehydrogenase (LDH)	Microscopic Exam	Total Triiodothyronine (T3) [e]
Absolute Neutrophil Count	Carbon Dioxide [b]	*(If abnormal results are noted)* [c]	Free Thyroxine (FT4)
Absolute Lymphocyte Count	*(CO_2 or bicarbonate)*	Urine Pregnancy Test [a]	Thyroid Stimulating Hormone (TSH)
	Uric Acid		Blood for FBR
	Calcium		Blood for Correlative Studies
	Chloride		Cancer Antigen 15-3 (CA 15-3) [d]
	Glucose		Carbohydrate Antigen 19-9 (CA 19-9) [d]
	Phosphorus		Cancer Antigen 27-29 (CA 27-29) [d]
	Potassium		Cancer Antigen 125 (CA-125) [d]
	Sodium		Carcinoembryonic Antigen (CEA) [d]
	Magnesium		Chromogranin A (CgA) [d]
	Total Bilirubin		Prostate-Specific Antigen (PSA) [d]
	Direct Bilirubin *(If total bilirubin is elevated above the upper limit of normal)*		Thyroglobulin (Tg) [d]
	Total protein		5-Hydroxyindoleacetic acid (5-HIAA) [d]
	Blood Urea Nitrogen		*(24 hours in urine)*
	Creatinine [f]		

a. Perform on women of childbearing potential only. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required. Pregnancy tests (serum and/or urine) should be repeated if required by local guidance.
b. If considered standard of care in your region.
c. Institutional standards are acceptable.
d. Tumor marker assessment is not an additional study-related laboratory evaluation. The purpose is to collect information that may be a part of standard clinical assessment for certain tumor types.
e. Free T3 may be performed in place of Total T3 per local standards
f. GFR (measured or calculated) or CrCl can be used in place of creatinine.

Laboratory tests for screening or entry into the Second Course Phase should be performed within 10 days prior to the first dose of treatment. After Cycle 1, in both the Initial Treatment Phase and the Second Course Phase, pre-dose laboratory procedures can be conducted up to 72 hours prior to dosing unless otherwise noted on the flow charts.

Laboratory results must be reviewed by the investigator or qualified designee and found to be acceptable prior to each dose of trial treatment.

7.1.3.2 Pregnancy Test

All women who are being considered for participation in the trial, and who are not surgically sterilized or postmenopausal, must be tested for pregnancy within 72 hours prior to first dose of trial treatment or retreatment. Pregnancy tests (serum and/or urine tests) should be repeated if required by local guidelines. If a urine test is positive or not evaluable, a serum test will be required. Subjects must be excluded/discontinued from the trial in the event of a positive or borderline-positive test result.

7.1.3.3 Future Biomedical Research

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

- Blood for genomics use
- Leftover archival tumor tissue or leftover newly obtained biopsy sample
- Leftover correlative blood samples

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 final trial 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 24 months of treatment with pembrolizumab may discontinue treatment with the option of restarting treatment if they meet the criteria specified in Section 7.1.5.2.1. After discontinuing treatment following assessment of CR or 24 months of therapy, these subjects should return to the site for a Safety Follow-up Visit (described in Section 7.1.5.3.1) and then proceed to the Follow-Up Period of the study (described in Section 7.1.5.4).

7.1.4.1.1 Withdrawal From Future Biomedical Research

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

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

7.1.4.2 Blinding/Unblinding

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

7.1.4.3 Calibration of Critical Equipment

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

Critical Equipment for this trial includes:

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

See protocol-specific Administrative Binder, Procedures Manual, Pharmacy Manual, and SIM.

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 Period

Approximately 28 days prior to enrollment, potential subjects will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5.1. Visit requirements are outlined in Section 6.0 – Trial Flow Chart.

Subjects that have an archival tumor biopsy sample may sign a prescreening consent for characterization of PD-L1 status. After providing prescreening consent, subjects will be assigned a screening number. Subjects characterized with a PD-L1 positive tumor must subsequently provide written consent for the main study prior to performing any protocol specific procedure. As noted in Section 7.2, AEs will NOT be collected for subjects during this pre-screening period (for determination of archival tissue status) as long as that subject has not undergone any protocol-specified procedure or intervention beyond archive sample collection for PD-L1 characterization.

Subjects that do not have an archival tumor biopsy sample available must provide written consent for the main study before the newly obtained tumor biopsy or any other protocol-specified procedures can occur. After providing main study consent, subjects not already provided a screening number will be assigned a screening number.

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

- Laboratory tests are to be performed within 10 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. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required (performed by the local study site laboratory)
- Tumor collection and PD-L1 characterization are not required to be completed within 28 days prior to the first dose of trial treatment

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 Period Visit

Visit requirements are outlined in the Trial Flow Chart (Section 6.0). Specific procedure-related details are provided in Section 7.1.

7.1.5.2.1 Second Course Phase (Retreatment Period)

Subjects who stop pembrolizumab with SD or better may be eligible for up to an additional 1 year of pembrolizumab therapy if they progress after stopping MK-3745. 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 pembrolizumab after attaining an investigator-determined confirmed CR according to RECIST 1.1, and
        - Was treated for at least 24 weeks with pembrolizumab before discontinuing therapy, and
        - Received at least 2 treatments with pembrolizumab beyond the date when the initial CR was declared

OR

- Subject had SD, PR or CR and stopped pembrolizumab treatment after 24 months of study therapy for reasons other than disease progression or intolerability

AND

- Experienced an investigator-determined confirmed radiographic disease progression by RECIST 1.1 after stopping their initial treatment with pembrolizumab, and
- No new anticancer treatment was administered after the last dose of trial treatment, and
- The subject meets all of the safety parameters listed in the inclusion criteria and none of the safety parameters listed in the exclusion criteria, and
- The trial is ongoing

Subjects who restart treatment will be retreated at the same dose frequency as when they last received pembrolizumab. Treatment will be administered for up to 1 additional year.

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

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

7.1.5.3 Post-Treatment Visits

7.1.5.3.1 Safety Follow-Up Visit

The mandatory Safety Follow-Up Visit should be conducted approximately 30 days (±3 days) after the last dose of trial treatment or before the initiation of a new anti-cancer treatment, whichever comes first.

All AEs and concomitant medications within 30 days of last dose of trial treatment, regardless of when the Safety Follow-Up visit occurs should be recorded. After day 30, all SAEs and ECIs continue to be captured until 90 days after last dose of trial treatment or before initiation of a new anti-cancer treatment, whichever comes first. Subjects with an AE of Grade >1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new anti-cancer therapy, whichever occurs first.

Subjects who are eligible for retreatment with pembrolizumab (as described in Section 7.1.5.2.1) may have up to 2 safety follow-up visits, 1 after the Treatment Period and 1 after the Second Course Phase.

7.1.5.4 Follow-up Visits

Subjects who discontinue trial treatment for a reason other than disease progression in the First Course Phase will move into the Follow-Up Phase and should be assessed every 8 weeks (56 ±7 days) in the first 6 months, and every 12 weeks (±7 days) after Month 6, by radiologic imaging to monitor disease status. In the Second Course phase Follow-up assessments should be performed every 12 weeks (±7 days). Every effort should be made to collect information regarding disease status until the start of new anti-cancer therapy, disease progression, death, end of the study or if the subject begins retreatment with pembrolizumab as detailed in Section 7.1.5.2.1. 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 7.1.5.2.1 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.

7.1.5.4.1 Survival Status

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 every 12 weeks (± 4 weeks) to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

To ensure current and complete survival data is available at the time of database locks, updated survival status may be requested during the course of the study by the Sponsor. For example, updated survival status may be requested prior to but not limited to an external Data Monitoring Committee review, interim and/or final analysis. Upon Sponsor notification, all subjects who do not/will not have a scheduled study visit or study contact during the Sponsor defined time period will be contacted for their survival status (excluding subjects that have a previously recorded death event in the collection tool).

7.2 Assessing and Recording Adverse Events

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

Changes resulting from normal growth and development that do not vary significantly in frequency or severity from expected levels are not to be considered adverse events.

Examples of this may include, but are not limited to, teething, typical crying in infants and children and onset of menses or menopause occurring at a physiologically appropriate time.

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

Adverse events may occur during the course of the use of the Sponsor's product in clinical trials or within the follow-up period specified by the protocol, or prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

Adverse events may also occur in screened subjects during any pre-allocation baseline period as a result of a protocol-specified intervention, including washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

Progression of the cancer under study is not considered an adverse event unless it is considered to be drug related by the investigator.

All adverse events will be recorded from the time the consent form is signed through 30 days following cessation of treatment and 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.

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

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

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

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

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

All reports of overdose with and without an adverse event must be reported within 24 hours to the Sponsor either by electronic media or paper. Sponsor Contact information can be found in the Investigator Trial File Binder (or equivalent).

7.2.2 Reporting of Pregnancy and Lactation to the Sponsor

Although pregnancy and lactation are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them) that occurs during the trial or within 120 days of completing the trial, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier. All subjects who become pregnant 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. Sponsor Contact information 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 a new cancer (that is not a condition of the study);
- Is associated with an overdose;
- Is an other important medical event

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

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 from the time the consent is signed through 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, whether or not related to the Sponsor's product, 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).

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 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 recorded as such on the Adverse Event case report forms/worksheets and 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).

Events of clinical interest for this trial include:

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

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

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

3. Additional adverse events:

   irAEs as defined in Section 5.2.1.2.

   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. Lab results should be evaluated and subjects should be asked for signs and symptoms suggestive of an immune-related event. Subjects who develop an ECI thought to be immune-related should have additional testing to rule out other etiologic causes. If lab results or

symptoms indicate a possible irECI, then additional testing should be performed to rule out other etiologic causes. If no other cause is found, then it is assumed to be immune-related.

7.2.3.3 Protocol-Specific Exceptions to Serious Adverse Event Reporting

Efficacy endpoints as outlined in this section will not be reported to the Sponsor as described in Section 7.2.3 - Immediate Reporting of Adverse Events to the Sponsor, unless there is evidence suggesting a causal relationship between the drug and the event. Any such event will be submitted to the Sponsor within 24 hours either by electronic or paper media.

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

The 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.

Table 9 Evaluating Adverse Events

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

V4.0 CTCAE Grading	**Grade 1**	**Mild; asymptomatic or mid symptoms; clinical or diagnostic observations only; intervention not indicated.**
	Grade 2	**Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.**
	Grade 3	**Severe or medically significant but not immediately life-threatening; hospitalization or prolongation or hospitalization indicated; disabling; limiting self-care ADL.**
	Grade 4	**Life threatening consequences; urgent intervention indicated.**
	Grade 5	**Death related to AE**
Seriousness	A serious adverse event is any adverse event occurring at any dose or during any use of Sponsor's product that:	
	†**Results in death**; or	
	†**Is life threatening; or** places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred (Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.); or	
	†**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or	
	†**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not a serious adverse event. A pre-existing condition is a clinical condition that is diagnosed prior to the use of a Merck product and is documented in the subject'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) **or**	
	Is an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event. 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 test drug	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 there is another obvious cause of the AE. (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.

8.0 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, changes are made to primary and/or key secondary hypotheses, or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with International Conference on Harmonisation (ICH) Guideline E-9). Changes to exploratory or other non-confirmatory analyses made after the protocol has been finalized, along with an explanation as to when and why they occurred, will be listed in the Clinical Study Report (CSR) for the study. Post hoc exploratory analyses will be clearly identified in the CSR. No separate Statistical Analysis Plan (SAP) for the primary, secondary and exploratory endpoints will be issued for this study, however, a separate molecular profiling analysis plan will be developed to explicitly address exploratory biomarker objectives.

8.1 Statistical Analysis Plan Summary

This section contains a brief summary of the statistical analyses for this trial. Full detail is in the Statistical Analysis Plan (SAP) (Section 8.2).

8.1.1 Efficacy Analyses

The primary and key secondary endpoints, primary analysis population, and statistical methods that will be employed for the efficacy analyses are presented in Table 10 below**.**

The primary hypothesis will be evaluated separately in each disease indication by evaluating best ORR by RECIST 1.1. A sequential monitoring approach will be used following the time that a minimum of 6 subjects have had at least 1 post-baseline scan in each indication.

The Type-I error rate over the multiple evaluations within an indication will be controlled by the truncated sequential probability ratio test procedure at 0.08 (1-sided) [32].

Table 10 Summary of Analysis Strategy for Key Efficacy Endpoints

Endpoint/Variable (Description, Timepoint)	Statistical Method	Analysis Population	Missing Data Approach
Primary Hypothesis #1:			
Best ORR by RECIST 1.1 in each disease indication	Truncated sequential probability ratio test [32]	Full Analysis Set (FAS)	Missing observation counted as non-responder
Secondary Objectives – Within Indication			
PFS	Summary statistics using Kaplan-Meier method	FAS	Censored at last assessment
OS	Kaplan-Meier method	FAS	Censored at last assessment
DOR	Summary statistics using Kaplan-Meier method	All responders	Non-responders are excluded in analysis

8.1.2 Safety Analyses

The All-Subjects-as-Treated population will be employed for safety analyses. Immune related adverse experiences are prespecified as events of interest.

8.1.3 Power and Sample Size

Within each indication, the study will enroll a minimum of 6 subjects. Following the time that at least 6 subjects have had at least 1 post-baseline response assessment, a sequential monitoring procedure will be used to evaluate for efficacy and futility simultaneously based on the number of subjects with a confirmed or unconfirmed response according to the rules outlined in Figure 2, Table 11, and Table 12.

Depending on the enrollment rate, it is possible that more than 6 subjects may be enrolled prior to the first evaluation of efficacy or futility. Enrollment is expected to be continuous and will not be held within an indication.

Once at least 6 subjects are evaluable for confirmed or unconfirmed response, subsequent rules for pausing enrollment and future evaluations will be based on the boundaries identified by the sequential monitoring procedure. Approximately 22 subjects will be enrolled in each indication. The total sample size is approximately 440 subjects. Further details are provided in Section 8.2.7.

With 22 subjects per indication, this study provides 80% power to demonstrate that the best ORR induced by pembrolizumab exceeds 10% at an overall one-sided 8% alpha-level, if the true best ORR within an indication is 35%. The underlying treatment effect is regarded as clinically important in each of the indications studied. The calculation is based on the

binomialSPRT function in the gsDesign package and is carried out using R. The minimum criterion for success is that the lower bound of the repeated CI > 10% [33]. Given the underlying true rate, this may occur when at least 6/22 subjects develop a response. Further details are provided in Section 8.2.7.

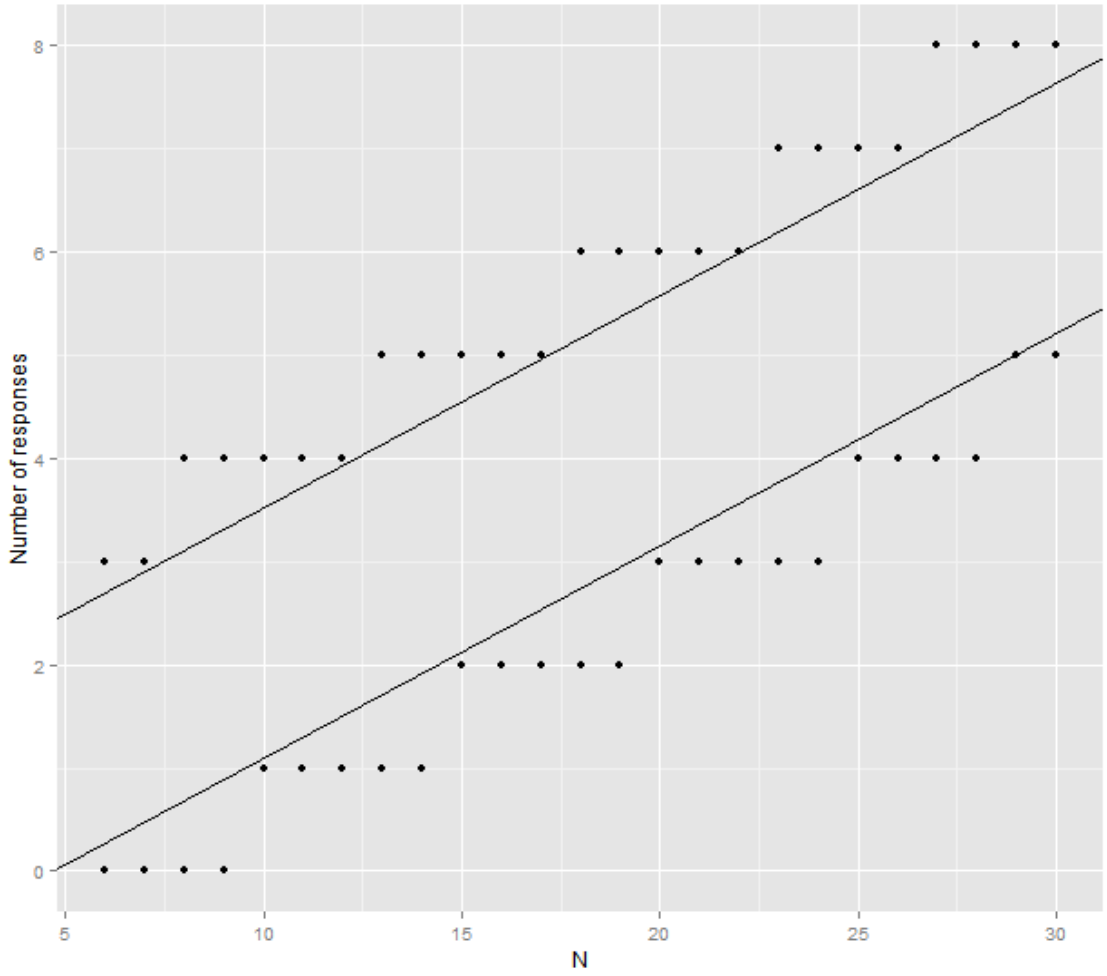

Figure 2 Sequential Monitoring Rules for Efficacy and Futility

Table 11 Decision Rules Based on Efficacy Bounds

Monitoring Point (# Subjects)	Minimum # Responders to Start Future Study Planning
6-7	3
8-12	4
13-17	5
18-22*	6
23-26	7
27-30	8
Design assumes overall Type I error of 8% (1-sided) and 80% power. *Success at the final analysis requires ≥6/22 subjects with a response.	

Table 12 Decision Rules Based on Futility Bounds

Monitoring Point (# Subjects)	Maximum # Subjects with Response to Declare Futility
6-9	0
10-14	1
15-19	2
20-24*	3
25-28	4
29-30	5
Design assumes overall Type I error of 8% (1-sided) and 80% power. *Success at the final analysis requires ≥6/22 subjects with a response.	

8.1.4 Interim Analysis

Multiple interim analyses may be performed in this study due to the sequential design of the trial. Results will be reviewed by the study team. The endpoint(s), timing, and purpose of the interim analysis are summarized in the Table 13. The decision rule and other statistical details are further described in Section 8.2.9.

Table 13 Summary of Interim Analysis Strategy

Key Endpoints for Interim Analysis	Timing of Interim Analysis	Purpose of Interim Analysis
Objective response rate (confirmed or unconfirmed)	Sequential monitoring approach	• Stop for futility • Go to future study planning

8.2 Statistical Analysis Plan

8.2.1 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, i.e., subjects, investigators, and Sponsor personnel will be aware of subject treatment assignments after each subject is enrolled and treatment is assigned.

The Clinical Biostatistics department will generate the allocation schedule(s) for study treatment assignment. Allocation will be implemented in an interactive voice response system (IVRS).

8.2.2 Hypotheses/Estimation

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

8.2.3 Analysis Endpoints

Efficacy and safety endpoints that will be evaluated for within- and/or between-treatment differences are listed below, followed by the descriptions of the derivations of selected endpoints.

8.2.3.1 Efficacy Endpoints

Efficacy endpoints that will be evaluated for are listed below, followed by the descriptions of the derivations of selected endpoints.

The primary efficacy endpoint is best ORR, defined as the proportion of subjects in the analysis population who have CR or PR based on assessments by the investigator, and confirmed per RECIST 1.1 at any time during the study. Response for the primary analysis will be determined by the investigator assessment, and a confirmation assessment is required per RECIST 1.1.

Secondary efficacy endpoints include: (1) DOR, defined as time from first RECIST 1.1 response to disease progression in subjects who achieve a PR or better based on assessments by the investigator, and confirmed per RECIST 1.1; (2) PFS, defined as the time from allocation to the first documented disease progression based on assessments by the

investigator, and confirmed per RECIST 1.1 or death due to any cause, whichever occurs first; and (3) OS, defined as the time from first dose of trial medication to the time of death due to any cause.

Additional supportive analyses of best ORR, DOR, and PFS will be conducted using modified RECIST 1.1 criteria, in which a confirmation assessment of disease progression must be obtained at least 4 weeks after the initial disease assessment indicating progressive disease.

8.2.3.2 Safety Endpoints

A description of safety measures is provided in Section 4.2.3.2.

The primary safety endpoints are AEs graded using CTCAE (Version 4.0) criteria. Safety will be assessed by quantifying the toxicities and grades experienced by subjects who have received pembrolizumab, including SAEs and ECIs. Immune related adverse experiences (irAEs) are prespecified as events of interest. Other safety endpoints include laboratory safety assessments, ECOG performance status, vital signs and physical examinations.

8.2.4 Analysis Populations

8.2.4.1 Efficacy Analysis Populations

The FAS population will serve as the primary population for the analysis of efficacy data in this study. The FAS population consists of all subjects within each indication who:

- Receive at least 1 dose of study treatment, and
- Have a baseline scan with measurable disease per RECIST 1.1

Subjects will be included in the treatment group to which they are allocated for the analysis of efficacy data. Details on the approach to handling missing data are provided in Section 8.2.5, Statistical Methods.

8.2.4.2 Safety Analysis Populations

The All Subjects as Treated (ASaT) population will be used for the analysis of safety data in this study. The ASaT population consists of all allocated subjects who received at least 1 dose of study treatment.

At least 1 laboratory or vital sign measurement obtained subsequent to at least 1 dose of study treatment is required for inclusion in the analysis of each specific parameter. To assess change from baseline, a baseline measurement is also required.

Details on the approach to handling missing data for safety analyses are provided in Section 8.2.5, Statistical Methods.

8.2.5 Statistical Methods

Statistical testing and inference for safety analyses are described in 8.2.5.2. Efficacy results that will be considered to be statistically significant after consideration of the strategy for controlling the Type I error are described in Section 8.2.6, Multiplicity. Nominal p-values may be computed for other efficacy analyses as a measure of strength of association between the endpoint and the treatment effect rather than formal tests of hypotheses. Unless otherwise stated, all statistical tests will be conducted at the α=0.05 (2-sided) level.

8.2.5.1 Statistical Methods for Efficacy Analyses

Efficacy will be evaluated separately in each cohort. For the primary efficacy endpoint investigator assessed RECIST 1.1 best ORR, the point estimate, repeated confidence interval, and adjusted p-value for testing the RECIST 1.1 response rate is greater than 10% for each disease indication will be provided using a truncated sequential probability ratio test [32], which is a specific instance of an exact binomial group sequential design for a single arm trial with a binary outcome. Subjects in the primary analysis population (FAS) without response data will be counted as non-responder. Interim decisions may be made based on confirmed or unconfirmed response assessments (see Sections 8.2.7 and 8.2.9). However, the final analysis (if enrollment in a given indication expands to 22 subjects) will require a confirmation assessment for all subjects who develop a CR or PR.

For PFS endpoint, Kaplan-Meier (KM) curves and median estimates from the KM curves will be provided as appropriate. Subjects without efficacy evaluation data or without survival data will be censored at Day 1.

Table 14 summarizes the key efficacy analyses.

Table 14 Analysis Strategy for Key Efficacy Variables

Endpoint/Variable (Description, Time Point)	Primary vs. Supportive Approach†	Statistical Method	Analysis Population	Missing Data Approach
Primary Hypothesis #1 – Within Indication				
Best ORR using RECIST 1.1 by site radiology assessment (each disease indication evaluated separately)	P	Truncated sequential probability test	FAS	Subjects with missing data are considered non-responders
Best ORR using modified RECIST 1.1 by site radiology assessment (each disease indication evaluated separately)	S	Truncated sequential probability test	FAS	Subjects with missing data are considered non-responders
Secondary Endpoints/Objectives– Within Indication				
PFS using RECIST 1.1 criteria by site assessment	P	Summary statistics using Kaplan-Meier method	FAS	Censored at last assessment
PFS using modified RECIST 1.1 criteria by site assessment	S	Summary statistics using Kaplan-Meier method	FAS	Censored at last assessment
OS	P	Kaplan-Meier method	FAS	Censored at last assessment
DOR by site assessment	P	Summary statistics using Kaplan-Meier method	All responders	Non-responders are excluded in analysis
Duration of modified RECIST 1.1 response (DOR) by site assessment	S	Summary statistics using Kaplan-Meier method	All modified RECIST 1.1 responders	Non-responders are excluded in analysis

† P=Primary approach; S=Secondary approach.

The strategy to address multiplicity issues with regard to multiple efficacy endpoints is described in Section 8.2.6, Multiplicity and Section 8.2.9, Interim Analyses.

8.2.5.2 Statistical Methods for Safety Analyses

Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs, laboratory tests, and vital signs. Safety summaries will be pooled across all indications.

Immune related adverse experiences are prespecified as events of interest. These events will be summarized in separate tables from other AEs by toxicity grade and will include the counts, percentage, and 95% CI. Any AE of unknown etiology associated with pembrolizumab exposure will be evaluated to determine if it is possibly an ECI of a potentially immunologic etiology (irECI). Other ECIs listed in Section 7.2.3.2 will also be summarized in the same manner as irAEs.

Adverse experiences (specific terms as well as system organ class terms) and predefined limits of change in laboratory, and vital sign parameters that are not pre-specified as events of interest will be summarized with descriptive statistics (counts, percentage, mean, standard deviation, etc.).

Continuous measures such as changes from baseline in laboratory, and vital signs parameters that are not pre-specified as events of interest will be summarized using descriptive statistics (mean, standard deviation, etc.) for baseline, on-treatment, and change from baseline values.

8.2.5.3 Summaries of Baseline Characteristics, Demographics, and Other Analyses

8.2.5.3.1 Demographic and Baseline Characteristics

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

8.2.6 Multiplicity

The false positive rate for testing the primary efficacy endpoint in each disease indication is controlled at 0.08 (1-sided) for each cohort. No additional multiplicity adjustment is required because each disease indication will be evaluated independently.

8.2.7 Sample Size and Power Calculations

Efficacy

Within each indication, the study will enroll a minimum of 6 subjects. Following the time that at least 6 subjects have had at least 1 post-baseline response assessment, a sequential monitoring procedure will be used to evaluate for efficacy and futility simultaneously based on the number of subjects with a confirmed or unconfirmed response according to the rules outlined in Figure 2, Table 11, and Table 12.

Enrollment will not be suspended at 6 subjects for the initial evaluation of efficacy.

Once at least 6 subjects are evaluable for confirmed or unconfirmed response, subsequent rules for pausing enrollment and future evaluations will be based on the boundaries identified by the sequential monitoring procedure. If 0 out of the first 6 subjects with a post-baseline evaluation have a confirmed or unconfirmed response following the first post-baseline assessment, then enrollment will be paused in that indication. The first 6 subjects and any additional subjects enrolled up to the time that the first 6 subjects are evaluated will continue to be followed for response. If the required number of subjects subsequently develop a confirmed or unconfirmed response to continue enrollment according to Figure 2, Table 11, and Table 12, then enrollment may resume in that indication. If ≥1 of the first 6 subjects with a post-baseline evaluation have a confirmed or unconfirmed response, then enrollment

will continue. Depending on the enrollment rate, additional monitoring may be performed according to the boundaries defined in Figure 2, Table 11, and Table 12 until approximately 22 subjects is enrolled within an indication.

If at any time during the trial, the efficacy boundary is crossed for a given indication, enrollment will continue to 22 subjects and subsequent trial planning may be initiated.

If enrollment within an indication is so rapid that 22 subjects are assigned a screening slot for potential enrollment at the time that the first 6 subjects are evaluable for response, then no sequential monitoring will be performed. If enrollment within an indication is so slow that a cohort is unlikely to complete within a reasonable amount of time, a cohort may be closed (e.g. low prevalence of PD-L1 such that fewer than 3 PD-L1 positive subjects are enrolled within a cohort after approximately 6 months of screening activity from all sites).

With an approximate maximum of 22 subjects enrolled within each indication, the study provides 80% power to demonstrate that the best ORR induced by pembrolizumab exceeds 10% at an overall one-sided 8% alpha-level, if the true best ORR is 35%. The null hypothesis of 10% is based on the assumption that the population for each indication is expected to consist of subjects with incurable solid tumors that have failed multiple lines of standard therapy. The best ORR for the limited treatment options available in these subject populations is generally <10%. The alternative best ORR is determined to be a clinically meaningful improvement over other standard treatment options within each studied indication. The calculation is based on the binomialSPRT function in the gsDesign package and is carried out using R assuming a null best ORR of 10%, an alternative best ORR of 35%, type I error of 0.08 and type II error of 0.2 (binomialSPRT (p0=0.1, p1=0.35, alpha=0.08, beta=0.2, minn=6, maxn=22)).

For the final analysis, the response assessment will be based on confirmed best ORR. The adjusted p-value and repeated confidence interval will be computed using sequential methods outlined by Jennison and Turnbull (2000) [33]. The minimum criterion for success is that the lower bound of the adjusted CI > 10%. Given the underlying true rate, this may occur when at least 6/22 subjects develop a confirmed PR or CR. Table 15 summarizes the power under various assumptions.

If the optional exploratory efficacy objective of best ORR per RECIST 1.1 based on central radiology review, best ORR per RANO criteria (GBM cohort), or best ORR per PCWG2 (prostate cancer cohort) is evaluated in an indication, and if fewer than 22 subjects in the respective indication have centrally confirmed measurable disease at baseline in that indication, then additional subjects may be enrolled to ensure that at least 22 subjects with centrally confirmed measurable disease are evaluable for the applicable central radiologist response assessment.

Table 15 Operating Characteristics of the Sequential Monitoring Approach

True Response Rate (RR)	Probability of Stopping for Futility	Probability of Go at end of Study	Average Sample Size
10%	0.92	0.05	9.9
15%	0.76	0.15	12.6
20%	0.57	0.31	15.2
25%	0.39	0.50	17.3
30%	0.25	0.67	18.9
35%	0.14	0.80	20.1
40%	0.08	0.89	20.9
45%	0.04	0.95	21.4
50%	0.02	0.97	21.7

Because the sample size within each indication is 22 subjects (assuming no additional subjects needed for the optional exploratory objective evaluation) the sample size for the entire study is approximately 440 subjects.

Safety

The probability of observing at least 10 subjects with a Grade 3-5 immune related in this study depends on the number of subjects treated and the underlying percentage of subjects with irAEs in the study population. If the underlying incidence of Grade 3-5 irAE is 10%, there is a 77% chance of observing at least 10 subjects with irAEs among the minimum 120 subjects enrolled in the study across all indications, whereas if the underlying incidence is 5% there is a 7.8% chance of observing at 10 occurrences or irAEs. Table 16 provides the point estimate and 95% CI for the underlying percentage of subjects with irAEs given various hypothetical numbers of subjects with irAEs and sample size across indications.

Table 16 Point Estimate and 95% CI for Hypothetical Number of Subjects with a Grade 3-5 irAE

Number of Subjects with Grade 3-5 irAE	Number of Subjects	Point Estimate	95% CI†
10	120	8.3%	(4.1%, 14.8%)
15	120	12.5%	(7.2%, 19.8%)
20	120	16.7%	(10.5%, 24.6%)
10	220	4.5%	(2.2%, 8.2%)
15	220	6.8%	(3.9%, 11.0%)
20	220	9.1%	(5.6%, 13.7%)
10	320	3.1%	(1.5%, 5.7%)
15	320	4.7%	(2.6%, 7.6%)
20	320	6.3%	(3.9%, 9.5%)
10	440	2.3%	(1.1%, 4.1%)
15	440	3.4%	(1.9%, 5.6%)
20	440	4.5%	(2.8%, 6.9%)

† Based on the 2-tailed exact confidence interval of a binomial proportion (Clopper and Pearson, 1934) [34].

8.2.8 Subgroup Analyses and Effect of Baseline Factors

No subgroup analysis is planned.

8.2.9 Interim Analyses

Multiple interim analyses may be performed in this study due to the sequential design of the trial. Results will be reviewed by the study team. The primary best ORR endpoint will be used for all interim decision-making with or without a confirmation assessment; however, a confirmation assessment is required for the final best ORR analyses after 22 subjects are enrolled in a cohort. For purpose of interim monitoring, subjects who are still on study but without a post baseline scan will be excluded from the analyses specified in Table 14. The decision rule and other statistical details are further described in Section 8.2.7.

8.2.10 Compliance (Medication Adherence)

A day within the study will be considered an On-Therapy day if the subject receives the study medication infusion. The number of Days Should be on Therapy is the total number of days from the first day of study medication to the date of the last dose of study medication. For each subject, percent compliance will then be calculated using the following formula:

$$\text{Percent Compliance} = \frac{\text{Number of Days on Therapy}}{\text{Number of Days Should be on Therapy}} \times 100$$

Summary statistics will be provided on percent compliance by treatment group for the FAS population.

8.2.11 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 17.

Table 17 Product Descriptions

Product Name & Potency	Dosage Form
Pembrolizumab 100 mg/4 mL	Solution for Infusion

9.2 Packaging and Labeling Information

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

Vials will be provided in an open label fashion for subject 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 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.

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 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 discarding 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 DNA and blood and tumor tissue specimen(s) collected in the current trial will be used to study various causes for how subjects may respond to a drug/vaccine. The DNA and blood and tumor tissue specimen(s) will be stored to provide a resource for future trials conducted by Merck focused on the study of biomarkers responsible for how a drug/vaccine enters and is removed by the body, how a drug/vaccine works, other pathways a drug/vaccine may interact with, or other aspects of disease. The specimen(s) may be used for future assay development and/or drug/vaccine development.

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

3. Summary of Procedures for Future Biomedical Research

a. Subjects for Enrollment

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

b. Informed Consent

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

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

Subjects are not required to participate in the Future Biomedical Research sub-trial in order to participate in the main trial. Subjects who decline to sign the Future Biomedical Research informed consent will not have the specimen collected nor will they be discontinued from the main trial.

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

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

c. eCRF Documentation for Future Biomedical Research Specimens

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

d. Future Biomedical Research Specimen Collections

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

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

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

4. Confidential Subject Information for Future Biomedical Research

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

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

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

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

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

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

5. Biorepository Specimen Usage

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

Analyses utilizing the Future Biomedical Research specimens may be performed by Merck, or an additional third party (e.g., a university investigator) designated by Merck. The investigator conducting the analysis will be provided with double coded specimens.

Re-association of analysis results with corresponding clinical data will only be conducted by the Merck Entrusted Keyholder. Any contracted third party analyses will conform to the specific scope of analysis outlined in this sub-trial. Future Biomedical Research specimens remaining with the third party after the specific analysis is performed will be returned to the sponsor or destroyed and documentation of destruction will be reported to Merck.

6. Withdrawal From Future Biomedical Research

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

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

7. Retention of Specimens

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

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

8. Data Security

Separate databases for specimen information and for results from the Future Biomedical Research sub-trial will be maintained by Merck. This is done to separate the future exploratory test results (which include genetic data) from the clinical trial database thereby maintaining a separation of subject number and these results. The separate databases are accessible only to the authorized Sponsor and the designated trial

administrator research personnel and/or collaborators. Database user authentication is highly secure, and is accomplished using network security policies and practices based in international standards (e.g., ISO17799) to protect against unauthorized access. The Merck Entrusted Keyholder maintains control over access to all specimen data. These data are collected for future biomedical research purposes only as specified in this sub-trial will not be used for any other purpose.

9. Reporting of Future Biomedical Research Data to Subjects

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

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

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

10. Gender, Ethnicity and Minorities

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

11. Risks Versus Benefits of Future Biomedical Research

For future biomedical research, risks to the subject have been minimized. 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.

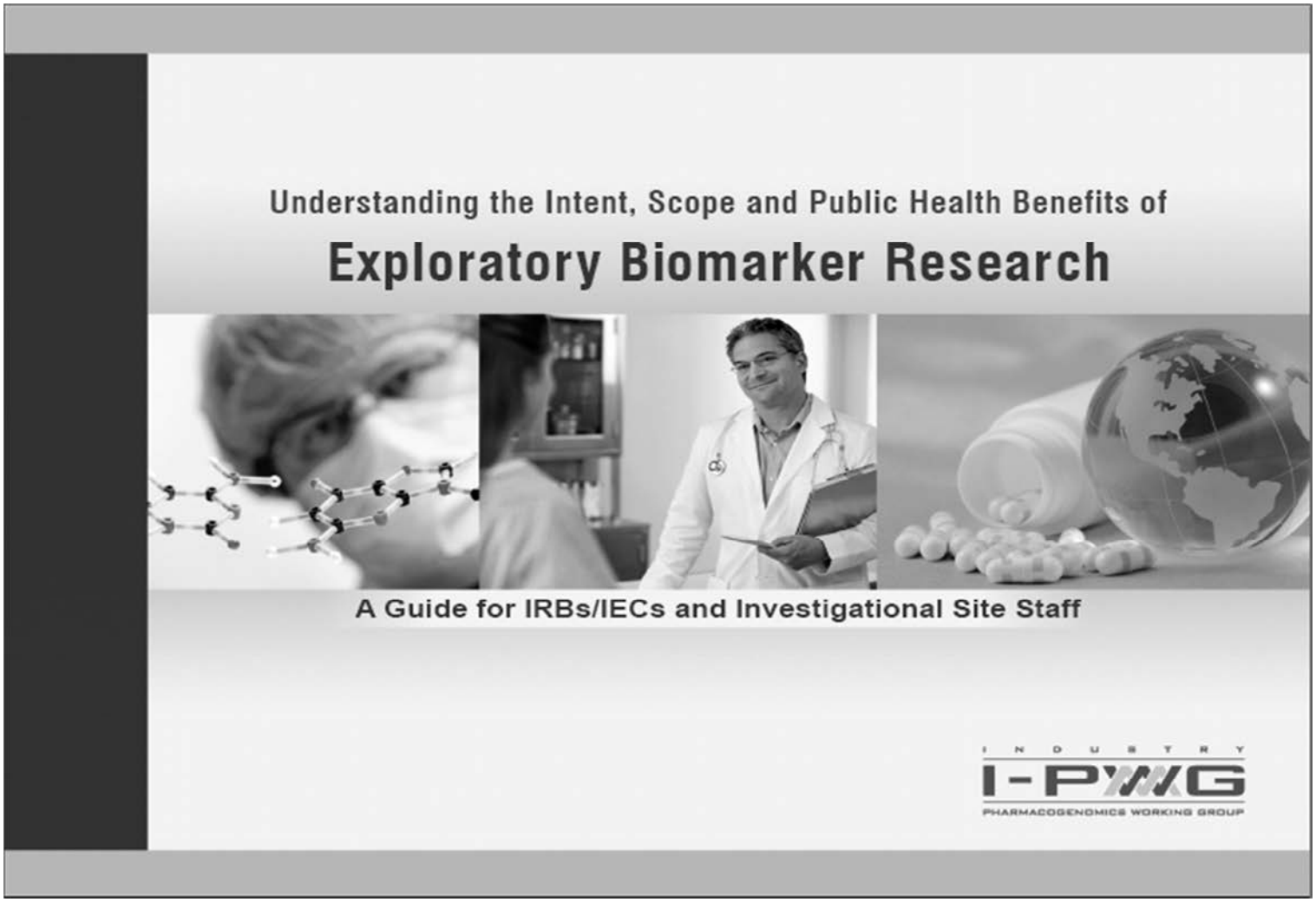
13. Questions

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

14. References

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

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



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

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

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

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

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

2. Why is Biomarker Research Important?

Importance to Patients and Public Health

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

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

Importance to Drug Development

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

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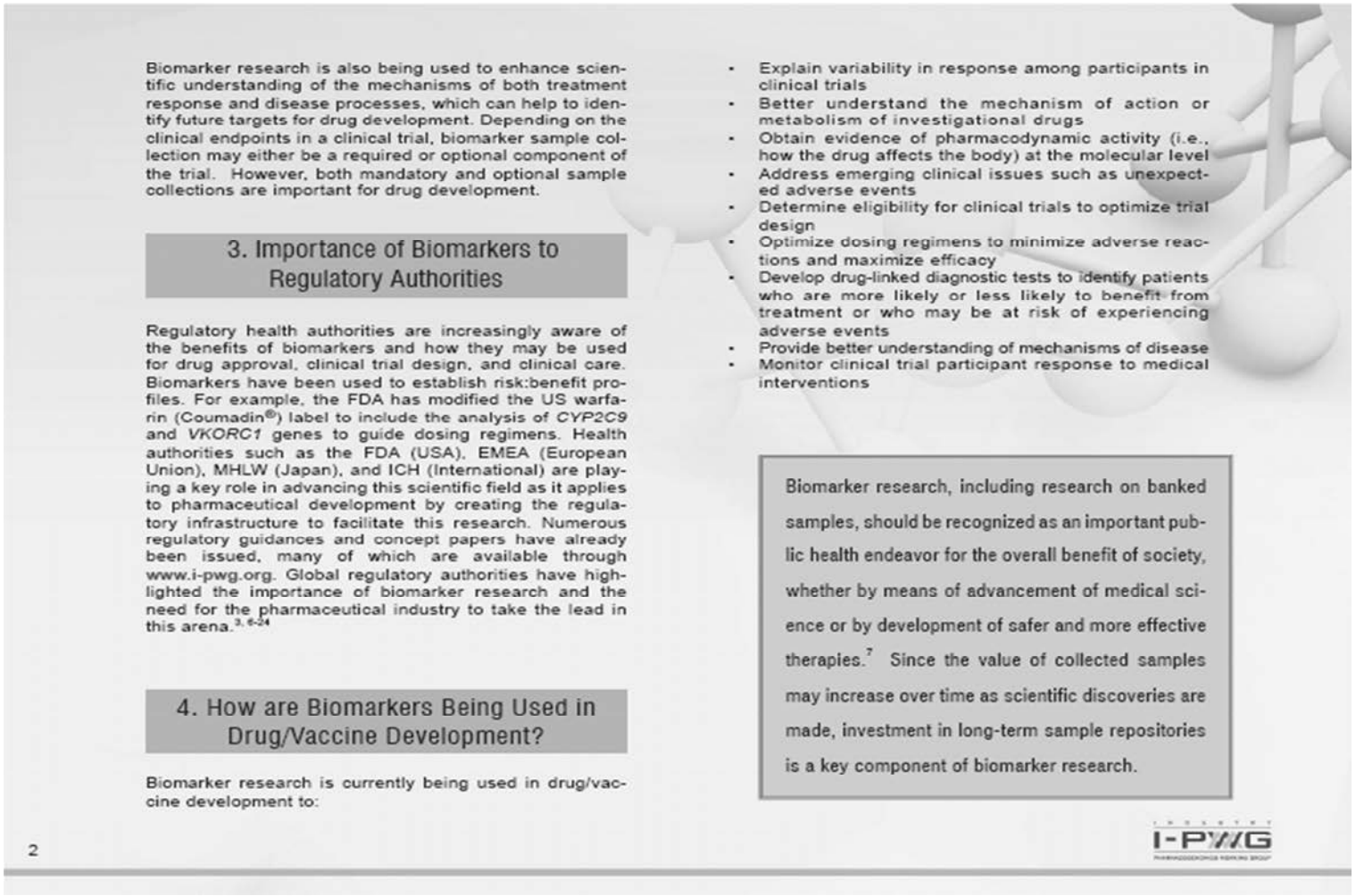

Biomarker research is also being used to enhance scientific understanding of the mechanisms of both treatment response and disease processes, which can help to identify future targets for drug development. Depending on the clinical endpoints in a clinical trial, biomarker sample collection may either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

3. Importance of Biomarkers to Regulatory Authorities

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

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

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

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

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

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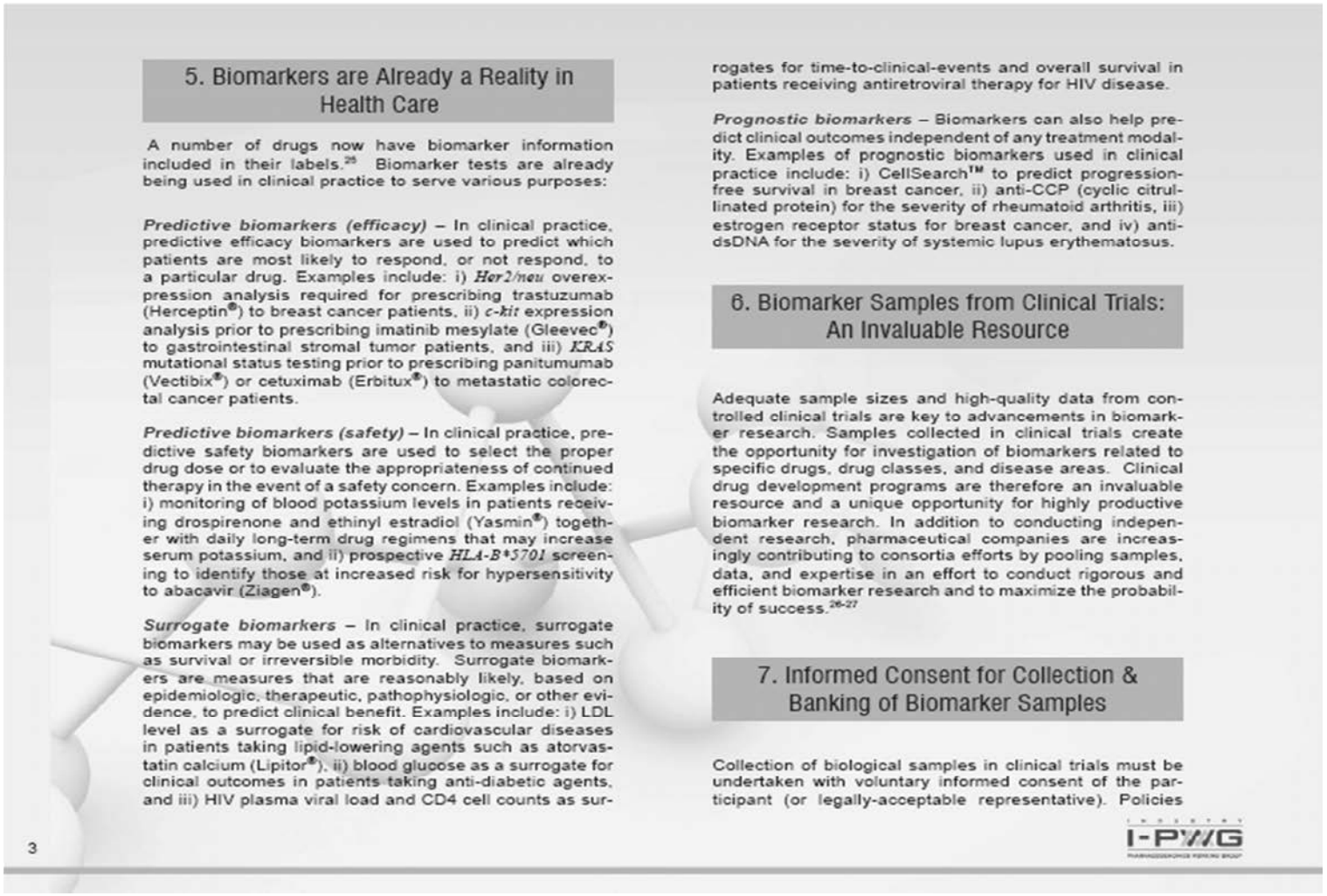

5. Biomarkers are Already a Reality in Health Care

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

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

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

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

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

6. Biomarker Samples from Clinical Trials: An Invaluable Resource

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

7. Informed Consent for Collection & Banking of Biomarker Samples

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

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and regulations for legally-appropriate informed consent vary on national, state, and local levels, but are generally based on internationally recognized pillars of ethical conduct for research on human subjects.[25-31]

Optional vs. Required Subject Participation

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

Consent for Future Research Use

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

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

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

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

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

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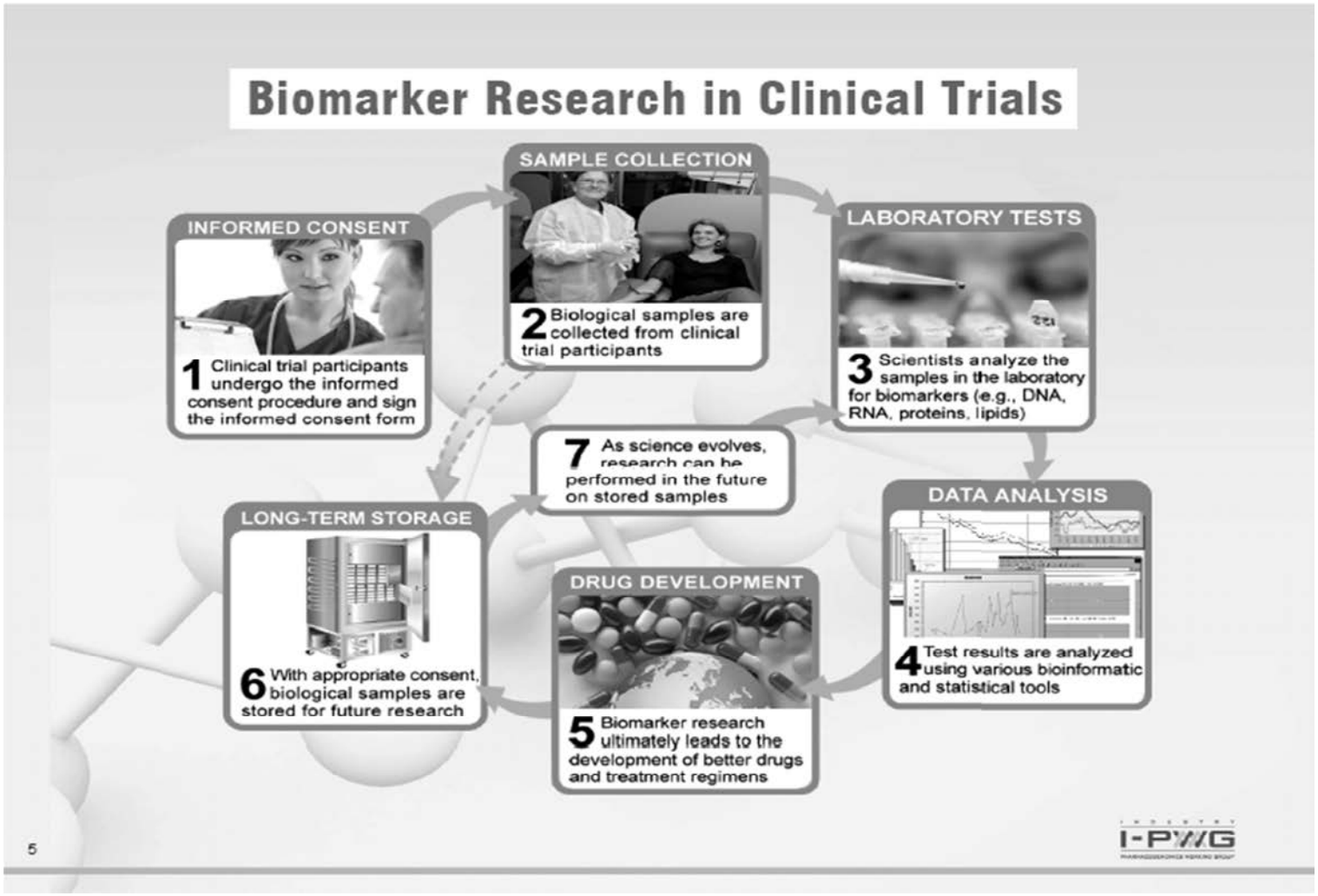
Biomarker Research in Clinical Trials
INFORMED CONSENT
1 Clinical trial participants undergo the informed consent procedure and sign the informed consent form
SAMPLE COLLECTION
2 Biological samples are collected from clinical trial participants
LABORATORY TESTS
3 Scientists analyze the samples in the 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*. 2006 and Article 29 Data Protection Working Party (an advisory committee to the European Commission on the European Data Protection Directive) have addressed these considerations in detail in relation to pharmacogenomic research data and provided a list of documents addressing the general issue of return of research results.[34-35]

10. Benefits and Risks Associated with Biomarker Research

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

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

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

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

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

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

11. Privacy, Confidentiality, and Patient Rights

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

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

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

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

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

12.Where to Get More Information?

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

13. What is I-PWG?

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

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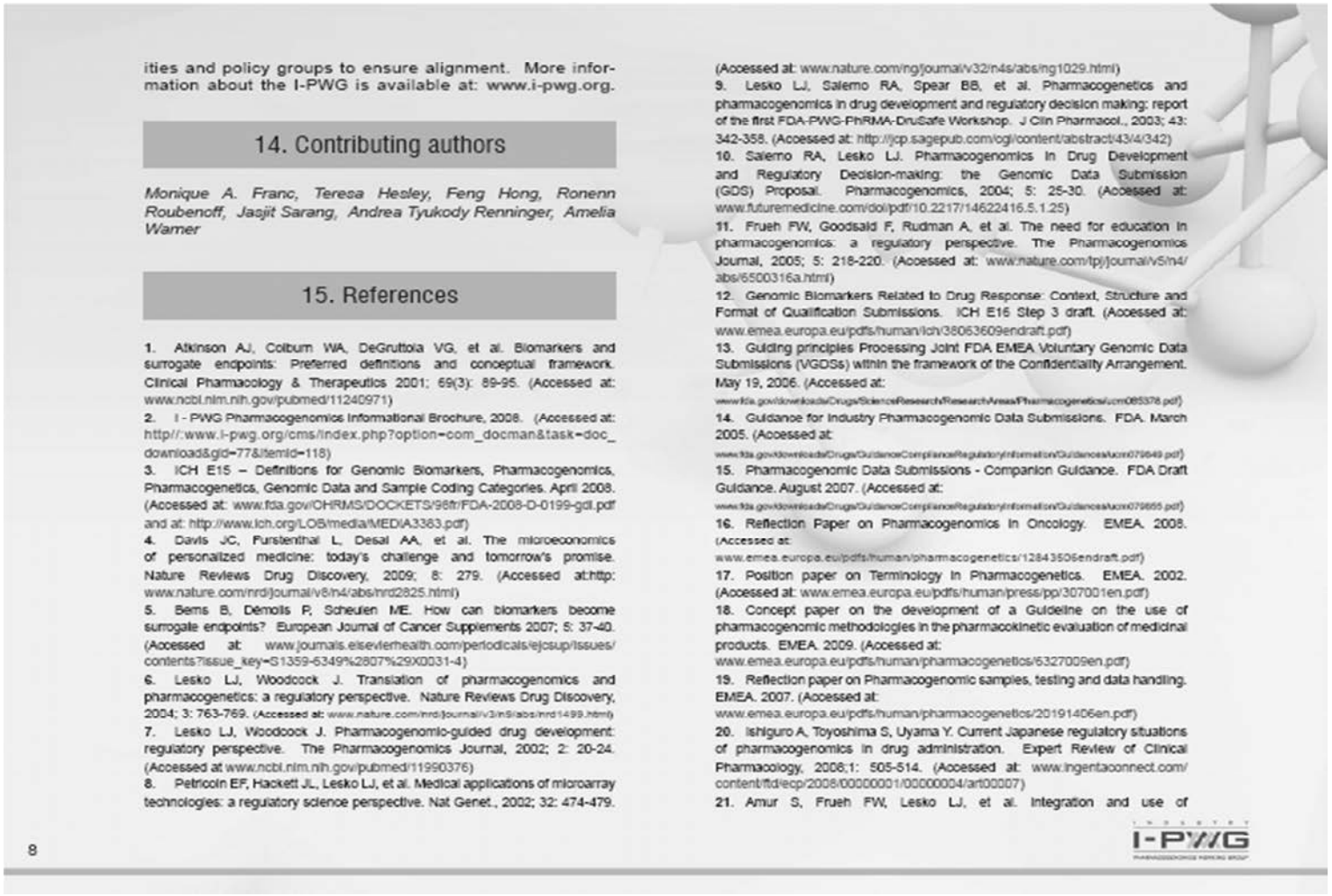

ities and policy groups to ensure alignment. More information about the I-PWG is available at: www.i-pwg.org.

14. Contributing authors

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

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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 V4.0 (CTCAE)

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

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:*

Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent R, Ford R, et al. New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1). Eur J Cancer 2009;45(2):228-47.

12.7 Updated Response Assessment Criteria for High-Grade Gliomas: Response Assessment in Neuro-Oncology Working Group

RANO criteria* will be used in this study to retrospectively confirm RECIST 1.1 response activity in GBM subjects using central review. While either CT or MRI may be utilized, as per RANO criteria, MRI is the preferred imaging technique for this cohort.

** As published in the Journal of Clinical Oncology:*

Wen PY, Macdonald DR, Reardon DA, Cloughesy TF, Sorensen AG, Galanis E., et al. Updated response assessment criteria for high-grade gliomas: Response assessment in neuro-oncology working group. J Clin Oncol 2010;28(11):1963-72.

12.8 Design and End Points of Clinical Trials for Patients With Progressive Prostate Cancer and Castrate Levels of Testosterone: Recommendations of the Prostate Cancer Clinical Trials Working Group

PCWG2 criteria* will be used in this study to retrospectively confirm RECIST 1.1 response activity in prostate cancer subjects using central review. The primary imaging modality for this cohort is CT for tumor assessment, with a bone scan to be considered at screening if consistent with local standard of care practices. Bone scans may be performed at subsequent time points when clinically indicated such as in the presence of new bone pain.

** As published in the Journal of Clinical Oncology:*

Scher HI, Halabi S, Tannock I, Morris M, Sternberg CN, Carducci MA, Eisenberger MA, et al. Design and end points of clinical trials for patients with progressive prostate Cancer and castrate levels of testosterone: Recommendations of the prostate Cancer clinical trials working group. J Clin Oncol 2008;26(7):1148-59.

12.9 List of Abbreviations

Abbreviation/Term	Definition
β-HCG	Serum β-human Chorionic Gonadotropin
5-HIAA	5-Hydroxyindoleacetic acid
AE	Adverse Event
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
aPTT	Activated Partial Thromboplastin Time
ASaT	All Subjects as Treated
AST	Aspartate Aminotransferase
BCG	Bacillus Calmette–Guérin
ß-HCG	Beta Human Chorionic Gonadotropin
CA 15-3	Cancer Antigen 15-3
CA 19-9	Carbohydrate Antigen 19-9
A 27-29	Cancer Antigen 27-29
CA-125	Cancer Antigen 125
CBC	Complete Blood Count
CD28	clusters of differentiation 28
CEA	Carcinoembryonic Antigen
CgA	Chromogranin A
CNS	Central Nervous System
CR	Complete Response
CrCl	Creatinine Clearance
CSR	Clinical Study Report
CT	Computed Tomography
CTCAE	Common Toxicity Criteria for Adverse Events
CTLA-4	Cytotoxic T-Lymphocyte-Associated Antigen-4
DNA	Deoxyribonucleic acid
DOR	Duration of Response
ECI	Events of Clinical Interest
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
ER	Estrogen Receptor
ERC	Ethics Review Committee
FAS	Full Analysis 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
FNA	Fine needle aspiration
FSH	Follicle-stimulating hormone
FT4	Free Thyroxine

Abbreviation/Term	Definition
GBM	Glioblastoma Multiforme
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
HBsAg	hepatitis B surface antigen
HCV	Hepatitis C virus
HER2	Human Epidermal Growth Factor Receptor-2
HIV	Human Immunodeficiency Virus
ICF	Informed Consent Form
ICH	International Conference on Harmonization
Ig	Immunoglobulin
IgC	Immunoglobulin constant domain
IgV	Immunoglobulin variable domain
IHC	Immunohistochemistry
INR	International Normalized Ratio
irAEs	Immune-related Adverse Events
irECI	Immune-related Events of Clinical Interest
IRB	Institutional Review Board
ITSM	Immunoreceptor Tyrosine-based Switch Motif
IUD	Intrauterine device
IV	Intravenous
Kg	kilogram
KM	Kaplan-Meier
LDH	Lactate Dehydrogenase
LHRH	Luteinizing-Hormone-Releasing Hormone
mAb	Monoclonal Antibody
mcL	microliter
MEL	Melanoma
mg	milligram
mg/kg	milligram per kilogram
mL	milliliter
MRI	Magnetic Resonance Imaging
mRNA	Messenger ribonucleic acid
MSD	Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
MTD	Maximum tolerated dose
N/A	Not Applicable
NCI	National Cancer Institute
NSAID	Non-Steroidal Anti-inflammatory Drug
ORR	Overall Response Rate
OS	Overall Survival
OTC	Over-the-counter
PCWG2	Prostate Cancer Clinical Trials Working Group 2
PD	Progressive Disease

Abbreviation/Term	Definition
PDCD1	Programmed cell death 1
PD-L1	Programmed Death - Ligand 1
PFS	Progression Free Survival
PGt	Pharmacogenetic
PK	Pharmacokinetic
PKPD	Pharmacokinetic-Pharmacodynamic
PO	Oral Administration
PR	Partial Response
PT	Prothrombin Time
PSA	Prostate Specific Antigen
RANO	Response Assessment in Neuro-Oncology
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic Acid
RR	Response Rate
Q2W	Every 2 Weeks
Q3W	Every 3 Weeks
SAE	Serious Adverse Events
SAP	Statistical Analysis Plan
SD	Stable Disease
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SIM	Site Imaging Manual
SOP	Standard Operating Procedures
T1DM	Type 1 diabetes mellitus
T3	Total Triiodothyronine
Tg	Thyroglobulin
TIL	Tumor-Infiltrating Lymphocytes
TSH	Thyroid Stimulating Hormone
ULN	Upper Limit of Normal
ZAP70	Zeta-chain-associated protein kinase

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	