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TITLE:

A Clinical Trial of Pembrolizumab (MK-3475) Evaluating Predictive Biomarkers in Subjects with Advanced Solid Tumors (KEYNOTE 158)

IND NUMBER: 127548

EudraCT NUMBER: 2015-002067-41

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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	Added guidelines for dose modification in the event of myocarditis and updated guidelines for several other conditions.	To align with the most current label and safety information for pembrolizumab.

ADDITIONAL CHANGE(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
6.0 7.1.1.11 7.1.9.3 7.1.9.4	Trial Flow Chart Survival Status Post-Trial Visit Requirements Survival Status	Added flexibility to perform survival follow-up as requested by the Sponsor, in addition to the regularly scheduled assessments.	To allow the Sponsor to collect information as needed to support ongoing analyses of the study survival data.
5.8.1	Discontinuation of Treatment	Reference to "Section 7.1.5.3 – Discontinued Subjects Continuing to be Monitored in the Trial" was removed.	This section of the protocol does not exist and was incorrectly referenced previously.
5.8.1	Discontinuation of Treatment	The sentence "Subjects may be allowed to begin treatment again if deemed medically appropriate, unless the subject's treatment assignment has been unblinded by the investigator/delegate and/or non-study treating physician" was removed.	This study does not have unblinding and therefore this sentence should not have been included.

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
5.8.2	Withdrawal from the Trial	Reference to "Section 7.1.4 – Other Procedures" was corrected to reference Section 7.1.8.	To ensure an accurate cross-reference to the appropriate section of the protocol.
6.1	Initial Treatment Phase Flowchart	The final Screening Phase of "Day -3 to 0" was changed to "-3 to -1".	To ensure appropriate timing for these screening assessments, as Day 0 does not exist.
4.1 4.2.2.1	Background Rationale for Fixed Dose Pembrolizumab	Text was changed and new text added in the pembrolizumab background and dose rationale sections.	To align with the most current label for pembrolizumab.
5.1.3	Subject Exclusion Criteria	New exclusion criteria were added: • Severe hypersensitivity to pembrolizumab and/or excipients. • Known history of active TB infection.	To align with the most current label and safety information for pembrolizumab.
Whole document		Formatting and typographical errors were corrected. Administrative changes such as renumbering references and updating the list of abbreviations were also made.	To ensure clear interpretation of the protocol.

1.0 TRIAL SUMMARY

Abbreviated Title	Pembrolizumab in Advanced Solid Tumors Analyzed for Predictive Biomarkers (KEYNOTE 158)
Trial Phase	II
Clinical Indication	The treatment of subjects with any of the following advanced (unresectable and/or metastatic) solid tumor types: **Tumor Types (Groups)**: (A) Anal Squamous Cell Carcinoma, (B) Biliary Adenocarcinoma (gallbladder or biliary tree (intrahepatic or extrahepatic cholangiocarcinoma) except Ampulla of Vater cancers) (C) Neuroendocrine Tumors (well- and moderately-differentiated) of the lung, appendix, small intestine, colon, rectum, or pancreas, (D) Endometrial Carcinoma (sarcomas and mesenchymal tumors are excluded), (E) Cervical Squamous Cell Carcinoma, (F) Vulvar Squamous Cell Carcinoma, (G) Small Cell Lung Carcinoma, (H) Mesothelioma, (I) Thyroid Carcinoma, (J) Salivary Gland Carcinoma (sarcomas and mesenchymal tumors are excluded), OR (K) Any advanced solid tumor, with the exception of colorectal carcinoma (CRC), which is Microsatellite Instability (MSI)-High (MSI-H). For each subject in Groups A-J, a tumor specimen must be provided for assessment of the following primary biomarkers: (1) Programmed Death Ligand 1 (PD-L1) expression as assessed by immunohistochemistry (IHC), (2) Gene expression profile (GEP) based on tumor RNA analysis, AND (3) Tumor MSI. Initially, subjects in Groups A-J will be enrolled regardless of the status of these three primary biomarkers (biomarker unselected phase). Following interim analyses of study results, subsequent enrollment of subjects in Groups A-J may be based on tumor expression of one or more primary biomarker (biomarker enrichment phase).
Trial Type	Interventional
Type of control	No treatment control
Route of administration	Intravenous

Trial Blinding	Unblinded Open-label
Treatment Groups	Pembrolizumab (MK-3475) 200 mg IV Q3W
Number of trial subjects	Approximately 200 (minimum) – up to approximately 1350 (maximum) subjects will be enrolled.
Estimated duration of trial	The sponsor estimates that the trial will require approximately 90 months from the time the first subject signs the informed consent until the last subject's last study-related phone call or visit.
Duration of Participation	Each subject will participate in the trial from the time the subject signs the Informed Consent Form through the final protocol-specified contact. After a screening phase of up to 42 days, eligible subjects will receive treatment with pembrolizumab (MK-3475) on Day 1 of each 3-week cycle. Treatment with pembrolizumab will continue until documented confirmed disease progression, unacceptable adverse event(s) (AE(s), intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw the subject, subject withdraws consent, pregnancy of the subject, noncompliance with trial treatment or required procedures, subject receives 35 administrations of pembrolizumab (approximately 2 years of treatment), or discontinuation for administrative reasons. Subjects who attain a complete response (CR) may consider stopping trial treatment if they meet criteria for discontinuing therapy. Subjects who receive a full 35-administration course of pembrolizumab, or who stop trial treatment before receiving 35 administrations of pembrolizumab for reasons other than disease progression or intolerability, or who attain a CR and stop trial treatment may be eligible for up to 17 administrations (approximately one year of retreatment (Second Course) after experiencing disease progression. The decision to retreat will be at the discretion of the investigator, provided that such a subject meets the criteria for treatment and the trial is ongoing. After the end of treatment, each subject will be followed for 30 days to monitor for AEs and events of clinical interest (ECI); subjects will be monitored for serious AEs (SAEs) 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 experiencing 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 (OS) until death, withdrawal of consent, or the end of the trial.

A list of abbreviations used in this document can be found in Section 12.4.

2.0 TRIAL DESIGN

2.1 Trial Design

This is a non-randomized, multi-site, open-label trial of pembrolizumab (MK-3475) in subjects with multiple types of advanced (unresectable and/or metastatic) rare cancers to be conducted in conformance with Good Clinical Practices. The primary purpose of this trial is to assess the Objective Response Rate (ORR) to treatment with pembrolizumab (MK-3475)

using Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1 (RECIST 1.1), as determined by independent central radiologic review. This trial will also evaluate the efficacy of pembrolizumab in subgroups defined by each of three prespecified primary biomarkers.

Subjects with any of following tumor types may be enrolled in this trial:

A. Anal Squamous Cell Carcinoma,

B. Biliary Adenocarcinoma (gallbladder or biliary tree (intrahepatic or extrahepatic cholangiocarcinoma) except Ampulla of Vater cancers),

C. Neuroendocrine Tumors (well- and moderately-differentiated) of the lung, appendix, small intestine, colon, rectum, or pancreas,

D. Endometrial Carcinoma (sarcomas and mesenchymal tumors are excluded),

E. Cervical Squamous Cell Carcinoma,

F. Vulvar Squamous Cell Carcinoma,

G. Small Cell Lung Carcinoma,

H. Mesothelioma,

I. Thyroid Carcinoma,

J. Salivary Gland Carcinoma (sarcomas and mesenchymal tumors are excluded),

AND

K. Any advanced solid tumor, with the exception of colorectal carcinoma (CRC), which is microsatellite instability (MSI)-high (MSI-H).

A tumor specimen for biomarker assessment will be required for enrollment of all subjects (Groups A-K). A new tumor specimen (defined as a tumor specimen collected since the completion of the most recent cancer therapy), if obtained as part of normal clinical practice (not solely for the purpose of screening for enrollment in this study) is preferred to archival samples. If collection of such a new tumor specimen for this study would require a procedure, not otherwise clinically indicated, that would create significant risk for the subject (including (but not limited to) biopsies of the brain, lung/mediastinum, pancreas, or endoscopic procedures extending beyond the esophagus, stomach or bowel), an archival specimen should be submitted. Tissue from tumor progressing at a site of prior radiation may be allowed for biomarker characterization, based on the Sponsor's approval.

For Groups A-J, the tumor tissue submitted for biomarker analysis must be a single tumor tissue specimen, or slides from a single tumor tissue specimen block, of sufficient quantity and quality to allow for central laboratory assessment of all three primary biomarkers (immunohistochemistry (IHC)-based tumor Programed Death Ligand 1 (PD-L1) expression, tumor Gene expression profile (GEP) RNA gene signature score, and tumor MSI status). For all Groups, any tumor tissue submitted for analysis of secondary and exploratory biomarkers must be from the same tumor tissue specimen used for primary biomarker assessment.

For the initial approximately 100 subjects enrolled in Group K, tumor tissue from the same specimen used for MSI assessment should also be submitted, if available, for assessment of

the GEP and PD-L1 primary biomarkers. For subsequent subjects enrolled in Group K, the tumor tissue must be submitted for biomarker analyses and must be a single tumor tissue specimen or slides from a single tumor tissue specimen block, must be from the same specimen used for MSI assessment, and must be of sufficient quantity and quality to allow for central laboratory retrospective assessment of tumor MSI status. If additional tumor tissue from this same block is available from subjects enrolled in Group K, it should be submitted for assessment of the GEP and PD-L1 primary biomarkers.

The trial will initially enroll subjects in Groups A-J regardless of primary biomarker status ("biomarker unselected"). After interim analyses of study results, one or more primary biomarker(s) may be used to enroll additional subjects in Groups A-J ("biomarker enrichment"). Cut-off values for tumor PD-L1 expression, GEP score, and the degree of MSI for biomarker enrichment will be prespecified prior to the initial interim analysis.

For each subject, measureable disease by RECIST 1.1 must be confirmed by independent central radiologic review. Subjects without centrally confirmed measurable disease at baseline will not be eligible for this trial.

A minimum of 200 subjects and a maximum of up to approximately 1350 subjects will be enrolled in this trial over a period of approximately 90 months. The trial may initially enroll approximately 50 subjects with each of the ten specified tumor types (Groups A-J) without biomarker enrichment. Approximately 50 additional subjects in each tumor type in Group (A-J) may subsequently be enrolled, either with or without biomarker enrichment. In addition, the study may enroll approximately up to approximately 350 subjects in the MSI-H Group K.

All subjects will receive a 200 mg dose of pembrolizumab (MK-3475) by intravenous (IV) administration every 3 weeks (Q3W). Subjects will be evaluated every 9 weeks (63 ±7 days) with radiologic imaging to assess response to treatment. After 12 months, radiographic imaging will be conducted every 12 weeks (84 ±7 days). RECIST 1.1 will be used to determine the primary efficacy endpoint of ORR. Immune-related RECIST (irRECIST, see Section 5.8.1) may be used by investigators for treatment decisions to account for tumor response patterns seen with pembrolizumab (e.g., tumor pseudoprogression). Secondary objectives include evaluation of safety, duration of response (DOR), progression-free survival (PFS), and overall survival (OS). Adverse events (AEs) will be monitored throughout the trial and graded in severity according to the guidelines outlined in the NCI Common Terminology Criteria for Adverse Events (CTCAE), version 4.0.

Treatment with pembrolizumab will continue until documented disease progression, unacceptable AE(s), intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw the subject, subject withdraws consent, pregnancy of the subject, noncompliance with trial treatment or procedure requirements, completion of 35 administrations of pembrolizumab (approximately 2 years of treatment), or discontinuation for administrative reasons. Subjects who attain a complete response (CR) may consider stopping trial treatment after receiving at least 8 administrations of pembrolizumab. In addition, subjects who complete a full 35-dose course of pembrolizumab (approximately 2 years of treatment), discontinue before 35 administrations of pembrolizumab for reasons other than disease progression or intolerability, or discontinue after attaining a CR and received at least 2 administrations of pembrolizumab after an initial CR, may be eligible for

up to 17 additional administrations of pembrolizumab (approximately one year of retreatment) if they subsequently experience radiologic disease progression. The decision to retreat will be at the discretion of the investigator, but retreatment can be considered only if no cancer treatment has been administered since the last dose of pembrolizumab, the subject still meets all parameters listed in the Inclusion/Exclusion criteria, and the trial remains open (refer to Section 5.8 for further details).

After the end of treatment, each subject will be followed for 30 days for AE and events of clinical interest (ECI) monitoring and 90 days for serious AE (SAE) monitoring. 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 OS until death, withdrawal of consent, becoming lost to follow-up or the end of the trial, whichever occurs first.

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.

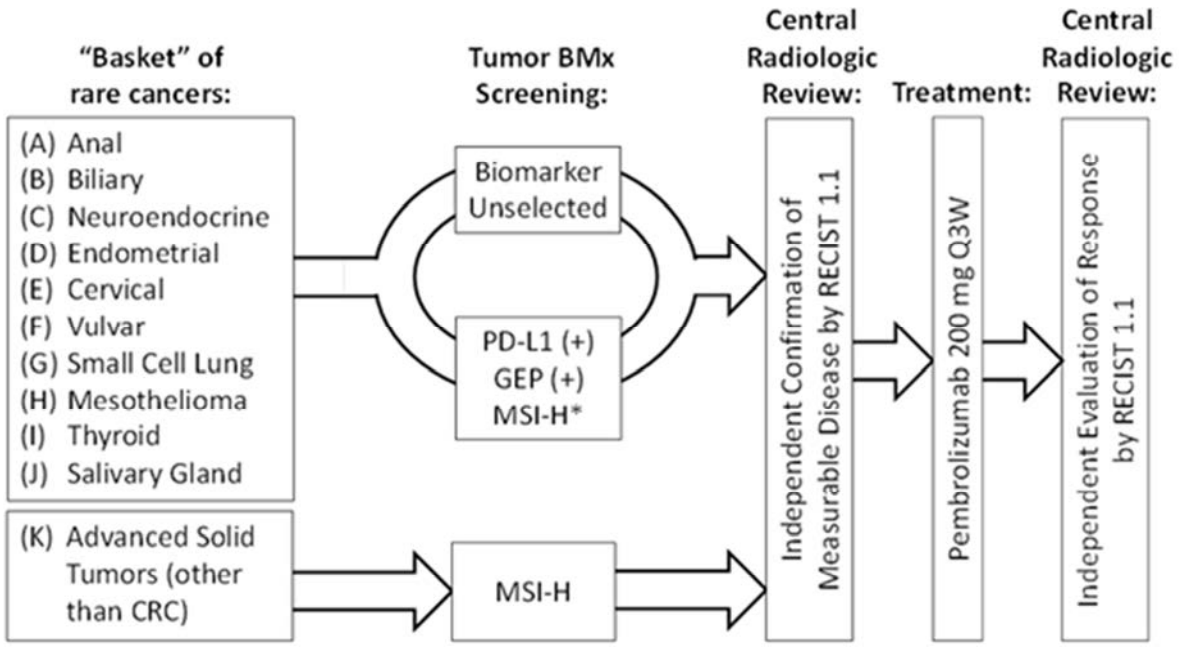

Figure 1 Trial Design

Subjects with any of the 10 advanced rare cancers (Groups A-J) and a tumor tissue specimen that is confirmed to be adequate for testing of all 3 primary biomarkers (BMxs) will be enrolled in the study, regardless of biomarker status (biomarker unselected). After interim analyses, one or more primary biomarker(s) may be used to enroll additional subjects in Groups A-J (biomarker enrichment). Subjects with any advanced solid tumor, with the

exception of CRC, that is MSI-H will be enrolled in Group K. After independent central radiologic confirmation of measurable disease, all subjects will be treated with pembrolizumab 200 mg IV Q3W, with evaluation of clinical response by RECIST 1.1, as assessed by independent central radiologic review.

*Selection of BMx(s) for biomarker enrichment may occur after interim analyses.

3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

Primary, secondary and exploratory objectives will be evaluated in a mixed population ("basket") of subjects with any of the tumor types listed below for which prior standard first-line treatment has failed. Patients must have progressed on or be intolerant to therapies that are known to provide clinical benefit.

A. Anal Squamous Cell Carcinoma,

B. Biliary Adenocarcinoma (gallbladder or biliary tree (intrahepatic or extrahepatic cholangiocarcinoma) except Ampulla of Vater cancers,

C. Neuroendocrine Tumors (well- and moderately-differentiated) of the lung, appendix, small intestine, colon, rectum, or pancreas,

D. Endometrial Carcinoma (sarcomas and mesenchymal tumors are excluded),

E. Cervical Squamous Cell Carcinoma,

F. Vulvar Squamous Cell Carcinoma,

G. Small Cell Lung Carcinoma,

H. Mesothelioma,

I. Thyroid Carcinoma,

J. Salivary Gland Carcinoma (sarcomas and mesenchymal tumors are excluded),

AND

K. Any MSI-H advanced solid tumor (except CRC).

3.1 Primary Objective(s) & Hypothesis(es)

Objective 1: To evaluate the ORR to pembrolizumab, based on RECIST 1.1 as assessed by independent central radiologic review, in biomarker-unselected subjects with any one of multiple types of advanced (metastatic and/or unresectable) solid tumors (Groups A-J)

Objective 2: To evaluate the ORR to pembrolizumab, based on RECIST 1.1 as assessed by independent central radiologic review, in biomarker-selected subjects with any one of multiple types of advanced (metastatic and/or unresectable) solid tumors (Groups A-K). The primary biomarkers to be evaluated are (1) tumor expression of PD-L1 by IHC (Groups A-J), (2) tumor GEP by RNA analysis (Groups A-J), and (3) tumor MSI-H (Groups A-K).

3.2 Secondary Objective(s) & Hypothesis(es)

Secondary Objectives

The following secondary objectives will be evaluated across the ten specified tumor types (Groups A-J):

(1) **Objective:** To evaluate DOR (based on RECIST 1.1 as assessed by independent central radiologic review) in subjects receiving pembrolizumab and the relationship between DOR and tumor PD-L1 expression and GEP score

(2) **Objective:** To evaluate PFS (based on RECIST 1.1 as assessed by independent central radiologic review) in subjects receiving pembrolizumab and the relationship between PFS and tumor PD-L1 expression and GEP score

(3) **Objective:** To evaluate OS in subjects receiving pembrolizumab and the relationship between OS and tumor PD-L1 expression and GEP score

The following secondary objectives will be evaluated across all tumor types (Groups A-K):

(4) **Objective:** To determine the safety and tolerability of pembrolizumab

(5) **Objective:** To evaluate DOR (based on RECIST 1.1 as assessed by independent central radiologic review) in subjects receiving pembrolizumab and the relationship between DOR and tumor MSI-H status

(6) **Objective:** To evaluate PFS (based on RECIST 1.1 as assessed by independent central radiologic review) in subjects receiving pembrolizumab and the relationship between PFS and tumor MSI-H status

(7) **Objective:** To evaluate OS in subjects receiving pembrolizumab and the relationship between OS and tumor MSI-H status

(8) **Objective:** To evaluate pembrolizumab pharmacokinetics (PK) for the 200 mg IV Q3W fixed dosing regimen that will be utilized in this trial

3.3 Exploratory Objectives

The following exploratory objectives will be evaluated across all tumor types (Groups A-K):

(1) **Exploratory Imaging Objective:**

a. To compare ORR, DOR, and PFS based on irRECIST with these same measures derived using RECIST 1.1, both as assessed by independent central radiologic review

(2) **Exploratory Clinical Objective**:

a. To describe the change in Patient Reported Outcome scores between baseline and post-baseline time-points overall and according to the subgroup of best overall response (CR, partial response [PR], stable disease [SD], progressive disease [PD]) using the EuroQol EQ-5D and EORTC QLQ-C30 instruments

(3) **Exploratory Biomarker Objectives:**

a. To analyze archival tumor specimens, collected at dates other than the date of collection of the tumor tissue submitted for assessment of the primary biomarkers, in order to investigate temporal changes in tumor biomarker expression

b. To investigate the relationship between response to pembrolizumab treatment and tumor DNA mutational burden as assessed by Whole Exome Sequencing (WES)

c. To investigate the relationship between predicted expression levels of tumor neoantigenic HLA-restricted peptides and response to pembrolizumab

d. To investigate changes in whole blood biomarker levels after the initial dose of pembrolizumab as possible pharmacodynamic (PD) biomarkers predicting clinical response to treatment

e. To evaluate the relationship between other candidate efficacy/resistance biomarkers and anti-tumor activity of pembrolizumab utilizing tumor tissue and blood sample analyses

f. To explore the relationship between genetic variation and response to the pembrolizumab treatment. Variation across the human genome may be analyzed for association with clinical data collected in this study

4.0 BACKGROUND & RATIONALE

4.1 Background

Pembrolizumab is a potent humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) with high specificity of binding to the programmed cell death 1 (PD-1) receptor, thus inhibiting its interaction with programmed cell death ligand 1 (PD-L1) and programmed cell death ligand 2 (PD-L2). Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an intravenous (IV) immunotherapy for advanced malignancies. Keytruda™ (pembrolizumab) is indicated for the treatment of patients across a number of indications. Refer to the Investigator's Brochure (IB)/approved labeling 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 to FoxP3+ regulatory T cells correlates with improved prognosis and long-term survival in solid malignancies, such as ovarian, colorectal, and pancreatic cancer; hepatocellular carcinoma; malignant melanoma; and renal cell carcinoma. Tumor-infiltrating lymphocytes can be expanded ex vivo and reinfused, inducing durable objective tumor responses in cancers such as melanoma.

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 *Pdcd1*) is an immunoglobulin (Ig) superfamily member related to cluster of differentiation 28 (CD28) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) that 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 (IgV-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. Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the immunoreceptor tyrosine-based switch motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3 zeta (CD3ζ), protein kinase C-theta (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, because both molecules regulate an overlapping set of signaling proteins [13] [14]. As a consequence, the PD-1/PD-L1 pathway is an attractive target for therapeutic intervention in many types of malignancies.

4.1.2 Pre-clinical and Clinical Trials

Therapeutic studies in mouse models have shown that administration of antibodies blocking the PD-1/PD-L1 interaction enhances infiltration of tumors by CD8+ T-cells and leads ultimately to tumor rejection. Anti-mouse PD-1 or anti-mouse PD-L1 antibodies have demonstrated anti-tumor responses as a monotherapy in murine models of squamous cell carcinoma, pancreatic carcinoma, melanoma and CRC. Blockade of the PD-1 pathway effectively promoted CD8+ T-cell infiltration into the tumor and the presence of IFN-γ, granzyme B and perforin, indicating that the mechanism of action involved local infiltration and activation of effector T-cell function *in vivo* [15] [16] [17] [18] [19] [20]. Experiments have confirmed the *in vivo* efficacy of PD-1 blockade as a monotherapy as well as in combination with chemotherapy in syngeneic mouse tumor models (refer to the IB).

In the initial clinical trial using pembrolizumab (KEYNOTE 001, KN001), 173 subjects with unresectable or metastatic melanoma with disease progression within 24 weeks of the last dose of ipilimumab or, if BRAF V600 mutation positive, prior treatment with a BRAF inhibitor, were randomized to receive pembrolizumab 2 mg/kg (n=89) or 10 mg/kg (n=84) IV once every 3 weeks until disease progression or unacceptable toxicity. The ORR was 24% in the 2 mg/kg arm, consisting of one CR and 20 PR, and similar ORR results were observed in the 10 mg/kg arm. Based on these results, in September, 2014, the United States Food and Drug Administration (FDA) granted accelerated approval to pembrolizumab for the treatment of subjects with unresectable or metastatic melanoma and disease progression following ipilimumab or, if BRAF V600 mutation-positive, a BRAF inhibitor.

4.1.3 Ongoing Clinical Trials

Ongoing clinical trials using pembrolizumab are being conducted in advanced melanoma, non-small cell lung cancer (NSCLC), bladder cancer, hematologic malignancies, and in a number of other advanced solid tumor indications. These studies are detailed in the IB.

In the KN028 trial (Clinicaltrials.gov: NCT02054806), the safety, tolerability, and antitumor activity of pembrolizumab is being assessed in subjects with a variety of malignancies, including the ten specific tumor types (Groups A-J) that will be evaluated in the trial described in this protocol. Of note, enrollment in KN028 is limited to subjects with tumor specimens with at least 1% of cells expressing PD-L1, as assessed by IHC using a prototype assay. The initial results from KN028 suggest that pembrolizumab is well tolerated in subjects with the ten specified malignancies (Groups A-J) included in the trial described in this protocol. In addition, as discussed below, the data from KN028 are being analyzed to inform on the prevalence, coexpression, and predictive value of tumor PD-L1 expression, GEP score, and MSI-H status as biomarkers predictive of pembrolizumab response.

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

4.2.1.1 Rationale for the Trial

The Phase II trial described in this protocol will evaluate the anti-tumor effect of pembrolizumab in a "basket" of rare malignancies and determine if any of three primary biomarkers predicts response to pembrolizumab treatment across multiple tumor types, regardless of specific tumor histology. The ultimate goal of this trial is to gain regulatory approval for pembrolizumab treatment across multiple different rare tumor types.

4.2.1.2 Rationale for the Selected Subject Population

This is a multicenter, nonrandomized, multi-cohort trial of pembrolizumab (MK-3475) in subjects with advanced solid tumors. Subjects with any of ten specified solid tumor types (Groups A-J) will be enrolled, as outlined in Section 2.1. These tumor types were selected because (1) each is a rare malignancy, (2) each represents a significant unmet medical need in the metastatic/refractory setting, (3) there is preliminary evidence of clinical response to pembrolizumab in these malignancies, and (4) preliminary data in these rare tumor indications (and in other tumor types) has identified three primary biomarkers that may be predictive of response to pembrolizumab.

In addition, up to approximately 350 subjects with advanced solid tumors (with the exception of CRC) may be enrolled (Group K) if their tumor is found to be MSI-H. This group is included in this study based on recently published data showing enhanced responses to pembrolizumab treatment in subjects with both MSI-H CRC and other MSI-H advanced cancers [21].

4.2.1.2.1 Rarity of the Malignancies Specified for Inclusion (Groups A-J)

The rarity of certain advanced-stage malignancies presents a challenge in drug development, especially when attempting to confirm the clinical activity of therapeutic agents such as pembrolizumab in such malignancies. Limited numbers of potential subjects may significantly prolong the time required for study accrual, especially for placebo-controlled Phase III studies that are commonly conducted for registration. Thus for rare tumors, it is not often feasible to conduct a randomized Phase III trial, thereby precluding this typical pathway to registration. However, it remains critical for these subjects to have access to potentially beneficial therapies such as pembrolizumab.

This study will initially enroll approximately 50 subjects with each of ten rare malignancies (Groups A-J): anal carcinoma, biliary adenocarcinoma (gallbladder or biliary tree (intrahepatic or extrahepatic cholangiocarcinoma) except Ampulla of Vater cancers, neuroendocrine tumors (well- and moderately-differentiated) of the lung, appendix, small intestine, colon, rectum, or pancreas), endometrial carcinoma (sarcomas and mesenchymal tumors are excluded), cervical carcinoma, vulvar carcinoma, small cell lung carcinoma, mesothelioma, thyroid carcinoma, and salivary gland carcinoma (sarcomas and mesenchymal tumors are excluded), independent of tumor primary biomarker testing results. This study may subsequently enroll approximately 50 additional subjects with each of these ten rare tumor types where eligibility may be based on tumor expression of one or more of the three specified primary biomarkers (biomarker enrichment).

Incidence and prevalence rates for these tumors have been derived using data from the US Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute (NCI) and 2015 US population projections and SEER*Stat software, AJCC staging and ICD-O-3 morphology codes. Based on a definition of rare cancers (incidence <6/100,000/year) by the Surveillance of Rare Cancers in Europe project [22], all of the specified tumor types planned for inclusion in this trial are rare, except for endometrial, small cell lung, and thyroid carcinomas (Table 1). However, for advanced stage disease (i.e., stage IV), all of these tumor types may be considered rare, with an annual incidence of <6/100,000. The threshold used for orphan disease designation in the US is a prevalence of <200,000. Using 5-year prevalence estimates, all of the tumor types (all stages) included in this trial meet this orphan threshold (Table 2). The prevalence of biomarker selected subgroups in these tumor types will be even lower.

Table 1 US Incidence Rates and Estimated 2015 Cases, by Stage at Diagnosis[a]

Cancer	Stage	SEER Incidence (per 100,000)	Estimated 2015 count
Anal Carcinoma	IV	0.041	132
	I-IV	0.61	1,968
Biliary Carcinoma	IV	1.12	3,598
	I-IV	2.39	7,688
Endometrial Carcinoma	IV	0.49	1,574
	I-IV	9.56	30,731
Cervical Carcinoma	IV	0.33	1,066
	I-IV	2.31	7,439
Vulvar Carcinoma	IV	0.097	311
	I-IV	1.16	3,731
Small Cell Lung Carcinoma	IV	4.62	14,832
	I-IV	7.45	23,944
Mesothelioma	IV	0.28	890
	I-IV	0.70	2,248
Thyroid Carcinoma	IV	0.58	1,858
	I-IV	7.20	23,149
Salivary Gland Carcinoma	IV	0.40	1,293
	I-IV	1.30	4,188
Neuroendocrine Tumors (including Carcinoid)	IV	0.21	686
	I-IV	2.23	7,163

[a]SEER Program (www.seer.cancer.gov) SEER*Stat Database: Incidence - SEER 18 Regs Research Data + Hurricane Katrina Impacted Louisiana Cases, Nov 2013 Sub (2000-2011) <Katrina/Rita Population Adjustment> - Linked To County Attributes - Total U.S., 1969-2012 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, Surveillance Systems Branch, released April 2014 (updated 5/7/2014 based on the November 2013 submission.

Table 2 US Estimated 5-year Prevalence as of 2015[b]

Cancer	5-yr prevalence (2015 cases)
Anal carcinoma	8,394
Biliary carcinoma	12,279
Endometrial carcinoma	144,975
Cervical Carcinoma	26,894
Vulvar Carcinoma	14,998
Small Cell Lung Carcinoma	35,217
Mesothelioma	3,299
Thyroid Carcinoma	112,396
Salivary Gland Carcinoma	18,493
Neuroendocrine Tumors (including Carcinoid)	50,980

[b]SEER Program (www.seer.cancer.gov) SEER*Stat Database: Incidence - SEER 9 Regs Research Data, Nov 2013 Sub (1973-2011) <Katrina/Rita Population Adjustment> - Linked To County Attributes - Total U.S., 1969-2012 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, Surveillance Systems Branch, released April 2014, based on the November 2013 submission.

4.2.1.2.2 Unmet Medical Need in the Malignancies Included in this Trial (Groups A-J)

A systematic literature review of randomized and non-randomized prospective clinical studies has been conducted to assess the clinical activity of relevant treatment comparators for each of the ten specified tumor types (Groups A-J) included in this trial. Table 3 summarizes the recommended anti-cancer therapy for advanced (metastatic or unresectable) disease in the first- and/or second-line setting(s) for theses tumors. These comparator recommendations are based on results from Phase III and sufficiently large prospective Phase II studies, as well as on National Comprehensive Cancer Network (NCCN) guidelines and European Society for Medical Oncology (ESMO) Clinical Practice Guidelines (and not on results from retrospective studies). Recommendations focus on second-line systemic therapy for the majority of tumors. In addition, comparators recommended for use in the first-line setting are included for subjects with anal and vulvar carcinoma, for which no Phase III or large Phase II study results could be identified. There are no NCCN or ESMO guidelines for treatment of vulvar carcinoma.

Table 3 Summary of Comparators and Associated Response Rates for the Malignancies Specified for Trial Inclusion

Tumor Type	Comparator	Line of Therapy	Response Rate
Anal Carcinoma	Cisplatin +5FU	1	N/A
	None recommended	2	N/A
Biliary Carcinoma	Gemcitabine + Cisplatin	1	26%
	None recommended	2	N/A
Neuroendocrine Tumors/Carcinoid:			
Carcinoid	Single-agent chemotherapy	?	(Unavailable)
Pancreas	Everolimus	2	No RR reported; median PFS: 11 mo
	Sunitinib	2	9.3%
Endometrial Carcinoma	Paclitaxel (other single-agent chemotherapy)	2	4% (cisplatin) to 27% (paclitaxel)
Cervical Carcinoma	Topotecan	2	18.6%
	Pemetrexed	2	15%
Vulvar Carcinoma	Cisplatin	1	(no standard 1l or 2L therapies)
Small Cell Lung Carcinoma	Topotecan	2	18.3-21.9%
Mesothelioma	Pemetrexed or Gemcitabine or Vinorelbine	2	18.7% PEM 16% vinorelbine
Thyroid Carcinoma	No standard	2	N/A (no standard)
Salivary Gland Carcinoma	Single-agent chemotherapy	2	10% (epirubicin) to 20% (vinorelbine)

In summary, in the ten rare advanced solid tumor types included in this trial, response rates from Phase III or large Phase II studies are either not available or poor (generally <10-20%) in the second-line setting, and it will be clinically appropriate to enroll subjects who have failed first-line (or higher) treatment in this study.

4.2.1.2.3 Preliminary Data Showing Response to Pembrolizumab in the Malignancies Included in this Trial

In the ongoing Phase Ib study KN028, subjects with any of twenty metastatic solid tumor types, including the ten tumor types specifically included in the current protocol, are being treated with pembrolizumab. Of note, enrollment in KN028 is contingent upon tumor expression of PD-L1 by at least 1% of cells, as assessed by IHC of a baseline formalin-fixed paraffin-embedded (FFPE) tumor sample using a prototype assay. For the ten tumor types included in the current protocol, the most current KN028 ORR data are presented in Table 4. These response rates to pembrolizumab appear to be higher than what has been generally reported in these groups of subjects with advanced tumors who have been treated with other agents after failing multiple prior therapies (or for whom no effective therapy is available). It

is anticipated that subjects with tumors positive for the three primary biomarkers being evaluated in this trial (see Section 4.2.3) may have a clinically meaningful overall response rate (ORR) even greater than that seen in biomarker unselected subjects.

Table 4 Initial Responses To Pembrolizumab Treatment In Study KN028

Tumor Types (Groups)	ORR (%)
A. Anal Carcinoma (n=25)	20.0
B. Biliary Carcinoma (n=23)	17.4
C. Neuroendocrine Tumors (well- and moderately-differentiated, including Carcinoid)) (n=14)	7.1
D. Endometrial Carcinoma (n=23)	13.0
E. Cervical Carcinoma (n=24)	8.3
F. Vulvar Carcinoma (n=9)	11.1
G. Small Cell Lung Carcinoma (n=19)	26.3
H. Mesothelioma (n=25)	28.0
I. Thyroid Carcinoma (n=22)	18.2
J. Salivary Gland Carcinoma (n=26)	11.5

Objective response rates (as of 23-Feb-2015) in subjects with tumor types included in this proposed trial treated with pembrolizumab are presented. Of note, tumors from subjects enrolled in KN028 had at least 1% PD-L1 expression as assessed by IHC using a prototype assay.

4.2.1.2.4 Rationale for Enrollment of Subjects with MSI-H Advanced Solid Tumors of Other Types (Group K)

In addition to enrolling subjects with specific tumor types as described above, this study will initially enroll approximately 100 subjects with any advanced solid tumor (with the exception of CRC) that is MSI-H. Subjects with CRC are excluded because the efficacy of pembrolizumab in subjects with MSI-H CRC is being studied under a separate protocol.

While the response rate to pembrolizumab in MSI-H tumors has been high in preliminary studies (see Section 4.2.1.3.3), the prevalence of MSI-H tumors may be low. By enrolling subjects with any solid tumor (with the exception of CRC) that is MSI-H, this cohort may be sufficiently large for accurate assessment of the clinical activity of pembrolizumab in MSI-H advanced solid tumors. In addition, this study may be able to demonstrate the utility of the MSI-H biomarker in predicting response to pembrolizumab agnostic of tumor histology.

Approximately 250 additional subjects with MSI-H advanced solid tumors (with the exception of CRC, endometrial cancer, and gastric cancer), will subsequently be enrolled. During this period, the trial will remain open to subjects with MSI-H cancer of any specific tumor type until a total of approximately 20 subjects with that specific tumor type have been enrolled. Specific tumor types that will be prioritized for enrollment include prostate, thyroid, ovarian, and small cell lung cancers. This should allow the assessment of the activity of pembrolizumab in types of tumors that have a low prevalence of MSI-H.

4.2.1.3 Rationale for the Three Primary Predictive Biomarkers

Based on data from hundreds of subjects in numerous pembrolizumab studies in multiple cancer types, each of the three primary biomarkers that will be evaluated in the trial proposed in this protocol is potentially predictive of response. The purpose of this trial is to determine if these biomarkers will identify subjects in the proposed basket of solid tumor types who will clinically respond to pembrolizumab.

4.2.1.3.1 Tumor PD-L1 Expression

Preliminary results from trial KN012, conducted in 4 indications (triple negative breast, head and neck, urothelial tract, and gastric cancers) suggest that the response rate to pembrolizumab treatment is enhanced in subjects with tumors expressing PD-L1, as assessed by IHC. Using a Youden-Index derived PD-L1 IHC cutpoint, the ORR in subjects with tumors with high PD-L1 expression was 45.5%, compared to 11.4% in subjects with tumors with lower PD-L1 expression. Additional data in subjects with NSCLC provides evidence that pretreatment tumor PD-L1 expression is a predictor of response to pembrolizumab. In subjects with evaluable tumor PD-L1 expression, a higher rate of radiologic responses by RECIST 1.1 occurred in subjects with tumors strongly positive for PD-L1 [23], further suggesting that tumor PD-L1 expression may be a predictive biomarker of clinical response to pembrolizumab (MK-3475).

Trial KN028, which is enrolling subjects with 20 different tumor types, including the ten specified tumor types included in this protocol, is using a prototype PD-L1 IHC assay that differs from the newer Dako IHC assay which has recently been developed as a companion diagnostic test and which will be used for assessment of tumor PD-L1 expression in the current protocol. Tumor specimens from KN028, including the ten specified tumor types being studied in this protocol (Groups A-J), are currently being reevaluated for PD-L1 expression using the Dako IHC assay. These data will be used to select a % staining cut-off for PD-L1 expression. This cut-off will be specified prior to the first interim analysis and will be used for all interim analyses of efficacy associated with this biomarker. This cut-off for tumor PD-L1 expression may also be used for biomarker enrichment-based enrollment as the study progresses.

4.2.1.3.2 Tumor Gene Expression Profile Score

Gene expression profile is a platform widely used by both clinical and laboratory researchers to perform mid-density gene expression profiling using RNA obtained from limited amounts of FFPE tumor tissue. The GEP technology uses a set of combination barcoded and single molecule imaging to count hundreds of unique RNA transcripts in a single reaction (up to 800 transcripts can be evaluated on a single platform). The GEP platform is very sensitive and capable of quantifying low input RNA amounts similarly to what can be detected by RT-PCR. This is important because RNA obtained from FFPE tumor tissue specimens is generally lower in abundance and more degraded relative to a newly obtained tissue specimen collected in RNA preservatives, and therefore an assay utilized for FFPE-based experiments must be able to evaluate gene expression levels from genes expressed at low abundance and from partially degraded RNA. The GEP platform has been previously applied in the clinical setting, specifically for analysis of a multi-gene expression marker set

predicting prognosis in breast cancer. Thus, the GEP platform may provide a path toward development of a multi-gene (signature) companion diagnostic assay that could potentially be applied in the clinic for making pembrolizumab treatment decisions.

The Merck research team initially identified a discovery set of 680 (657 biological genes and 23 housekeeping genes) genes that were derived from the following sources: 1) genes from an immune signature with co-expression to PD-L1 derived from a large set of human tumor expression data, 2) genes known to be involved in T cell biology, immune regulation, cellular markers of TILs and tumor-associated macrophages (TAMs) derived from the published literature, and 3) signatures from murine syngeneic tumor models with response to anti-PD-1 (mouse analog) mAb treatment. From this set of 680 genes and through the staged use of multiple cancer cohorts, a series of analyses identified a specific set of genes ("57-gene expression platform") that may be associated with pembrolizumab activity.

Because GEP data are currently available for only two of the specified tumor types included in this protocol, an analysis of cohorts available from KN012 (head & neck, gastric, bladder, and triple negative breast cancer) were combined with five cohorts from KN028 (anal, biliary, colorectal, esophageal, and ovarian cancers) to conduct a meta-analysis using a prototype version of a GEP score. The prototype scoring algorithm combines the normalized expression values of the 57 genes using a weighting derived from a penalized Cox regression of PFS (with penalty parameter selected by cross-validation) based on three of the cohorts from PN012. For this analysis, a cut-off of 0.05 for this GEP score was selected as an example since under the Bayesian hierarchical analysis it was associated with an expected ORR near 30% (see Table 5).

Table 5 Performance Characteristics of a Prototype Gene Expression Profile Predictive Biomarker

Clinical Utility Measures[a] at a Prototype GEP Cut-off of 0.05	**Posterior Median**	**90% Credible Interval**
Expected PPV	32%	(25%, 39%)
Expected NPV	91%	(85%, 95%)
Expected Prevalence	55%	(49%, 60%)

PPV: Response % at or above cut-off, NPV: Non-response % below cut-off
Prevalence: % of subjects at or above cut-off
[a] Posterior distribution of expected values determined by averaging histology specific values drawn from their joint posterior distribution

For illustrative purposes, a GEP score cutoff of 0.05 was selected and the analysis of PPV, NPV and prevalence was performed using all available GEP data from a variety of clinical pembrolizumab studies (see text).

Ribonucleic acids extracted from tumor tissue specimens from KN028 for the same ten specified tumor types being studied in this protocol (Groups A-J) are currently being assessed for GEP scoring. These data will be used to select a cut-off for the GEP score. This cut-off will be specified prior to the first interim analysis and will be used for all interim

analyses of efficacy associated with this biomarker. This cut-off for tumor GEP score may also be used for biomarker enrichment-based enrollment as the study progresses.

4.2.1.3.3 Tumor Microsatellite Instability

Microsatellite instability reflects defects in tumor DNA mismatch repair and is an indirect indicator of tumor DNA mutations. Recently presented data have demonstrated enhanced responses to pembrolizumab treatment in MSI-H CRC and non-CRC tumors, suggesting that MSI-H may be predictive of pembrolizumab response [21].

The reported prevalence of MSI-H is variable among the tumor types included in this protocol, although these reports are limited and utilize different assays and definitions of MSI-H, MSI-low, and microsatellite stabile (MSS). To investigate both the prevalence of MSI-H tumors and the potential predictive value of this biomarker in the malignancies included in this protocol, available tumor specimens from trial KN028 have recently been evaluated for MSI. Among 115 specimens available for testing from the ten tumor types included in this protocol, the prevalence of MSI-H was only 1.7% (2 of 115, with one of these two subjects responding to pembrolizumab). Because of this apparently low prevalence, Group K has been included to enroll subjects with advanced, MSI-H solid tumors (with the exception of CRC) to provide a larger basket of subjects in which to assess the predictive nature of MSI-H in pembrolizumab-treated patients.

4.2.2 Rationale for Dose Selection/Regimen

4.2.2.1 Rationale for Fixed Dose Pembrolizumab

The planned dose of pembrolizumab for this trial is 200 mg every 3 weeks (Q3W). The initial dose approved by the Food and Drug Administration (FDA) for treatment of melanoma subjects was 2 mg/kg Q3W. Currently, clinical trials evaluating pembrolizumab are using a fixed dose of 200 mg Q3W. The use of a fixed dose is based on PK findings summarized below.

The PK profile of pembrolizumab is consistent with that of other humanized monoclonal antibodies, which typically have a low clearance and a limited volume of distribution. A population PK model, which characterized the influence of body weight and other subject covariates on exposure using available data from 1139 subjects (from Keynote-001 and Keynote-002) has been performed. The majority of these subjects (1077; 94.6%) had advanced melanoma. The distribution of exposures from the 200 mg fixed dose were predicted to considerably overlap those obtained with the 2 mg/kg dose, and importantly, maintained individual subject exposures within the exposure range established in melanoma as associated with maximal clinical response. This comparison also demonstrated that the 200 mg Q3W regimen provided no substantive differences in PK variability (range of the distribution of individual exposures) as seen with weight-based dosing.

In translating to other tumor indications, similarly flat exposure-response relationships for efficacy and safety as observed in subjects with melanoma can be expected, as the anti-tumor effect of pembrolizumab is driven through immune system activation rather than through a direct interaction with tumor cells, rendering it independent of the specific tumor type. In addition, available PK results in subjects with melanoma, NSCLC, and other tumor types

support a lack of meaningful difference in pharmacokinetic exposures obtained at tested doses among tumor types. Thus the 200 mg Q3W fixed-dose regimen is considered an appropriate fixed dose for other tumor indications as well.

A fixed dose regimen will simplify the dosing regimen to be more convenient for physicians and to reduce potential for dosing errors. A fixed dosing scheme will also reduce complexity in the logistical chain at treatment facilities and reduce wastage.

4.2.3 Rationale for Endpoints

4.2.3.1 Efficacy Endpoints

4.2.3.1.1 Primary Efficacy Endpoint: RECIST-based Response Rate

The primary efficacy objective of this trial is to evaluate the anti-tumor activity of pembrolizumab in subjects with any of a "basket" of rare malignancies (biomarker unselected and biomarker enriched). Objective response rate will be used as the primary endpoint per RECIST 1.1 criteria (see Section 12.7), as assessed by independent central radiologic review. The central imaging vendor will be blinded to biomarker results to minimize any bias in response assessments.

4.2.3.1.2 Secondary Efficacy Endpoints

Secondary efficacy endpoints include (1) DOR, defined as the time from first documented evidence of CR or PR until disease progression or death due to any cause, whichever occurs first, (2) PFS, defined as the time from allocation to the first documented disease progression according to RECIST 1.1 or death due to any cause, whichever occurs first, and (3) OS.

Additional supportive analyses of ORR, DOR, and PFS will be conducted in which a confirmatory assessment of disease progression must be obtained at least 4 weeks after the initial disease assessment indicating PD (see Section 5.8.1).

4.2.3.1.3 Exploratory Efficacy Endpoints

4.2.3.1.3.1 irRECIST-Based Responses

The central imaging vendor will also assess responses using irRECIST (see Section 5.8.1). ORR, DOR, and PFS assessments determined using irRECIST will be compared with those derived using RECIST 1.1. The central imaging vendor will be blinded to biomarker results to minimize any bias during these irRECIST-based assessments.

4.2.3.1.3.2 Patient Reported Outcomes

EORTC QLQ-C30 and EQ-5D measure both efficacy and safety and are affected by both disease progression and treatment tolerability.

eEuroQoL EQ-5D

The eEuroQol-5D (eEQ-5D) is a standardized instrument for use as a measure of health outcome. The eEQ-5D will provide data for use in economic models and analyses including

developing health utilities or measuring quality-adjusted life-year. The five health state dimensions in this instrument include mobility, self-care, usual activities, pain/discomfort, and anxiety/depression [24]. Each dimension is rated on a three-point scale from 1 (extreme problem) to 3 (no problem). The eEQ-5D also includes a graded (0 to 100) vertical visual analog scale on which the subject rates his or her general state of health at the time of the assessment. The eEQ-5D must be completed by subjects before completing the EORTC QLQ-C30.

EORTC QLQ-C30

The EORTC QLQ-C30 instrument assesses the quality of life of cancer subjects. It has been translated and validated into 81 languages and used in more than 3,000 studies worldwide. It contains 5 functioning scales (physical, role, cognitive, emotional, and social), 3 symptom scales (fatigue, nausea, pain) and additional single symptom items. It is scored on a 4-point scale (1=not at all, 2=a little, 3= quite a bit, 4=very much). The EORTC QLQ-C30 instrument also contains 2 global scales that use 7-point scoring (1=very poor and 7=excellent).

4.2.3.2 Safety Endpoints

A secondary objective of this trial is to determine the safety and tolerability of pembrolizumab across subjects with the multiple advanced solid tumors included in this trial. Safety will be assessed in subjects who have received pembrolizumab by quantifying and grading reported AEs using CTCAE, Version 4.0. Attribution to drug, time-of-onset, duration of the event, resolution, and any concomitant medications administered will be recorded. AEs to be analyzed include but are not limited to all AEs, ECIs, SAEs, fatal SAEs, and laboratory changes.

4.2.3.3 Primary Biomarker Endpoints

Entry into this trial for subjects with any of the ten advanced solid tumor types (Groups A-J) will depend on the submission of a sufficient quantity of tumor tissue for testing by a central laboratory of the three potentially predictive tumor biomarkers: PD-L1 expression, GEP score, and MSI-H status. As the trial progresses, interim analyses will be conducted, after which tumor expression of one or more primary biomarker(s) may be required for enrollment of additional subjects in Groups A-J.

Subject entry into Group K will be dependent on MSI testing results, as described in the Procedures Manual, Section 4.0.

4.2.3.4 Exploratory Biomarker Research

Additional biomarker research to identify factors predictive of pembrolizumab response and resistance will be pursued in an exploratory manner. For example, proteomic, genomic and transcriptional analyses may be conducted using tumor specimens and blood samples. Analyses may also be conducted to identify novel targets for cancer immunotherapy.

Exploratory biomarkers to be investigated may include, but are not limited to the following:

4.2.3.4.1 Temporal Changes in Primary Biomarkers in Tumor Specimens

For each enrolled subject, any available archival tumor tissue from biopsies or surgical specimens collected at dates other than the date of collection of the tumor tissue submitted for assessment of the primary biomarkers will be requested. This tumor tissue will be used to assess changes in the three primary biomarkers (PD-L1 expression, GEP score, and MSI-H status) over time.

4.2.3.4.2 Tumor Mutational Burden

The relationship between tumor DNA mutation burden and response to pembrolizumab administration may be explored using DNA WES. WES analysis of whole blood DNA will be used as a control.

4.2.3.4.3 Predicted Tumor Mutated Neoantigen Presentation

Deoxyribonucleic whole exome sequencing data, tumor RNA sequencing analysis, and HLA phenotype may be used in combination to identify and possibly quantitate tumor neoantigenic peptides that may be recognized by anti-tumor T cells. Potentially immunogenic neoantigenic peptides might represent a biomarker more predictive of pembrolizumab response than tumor DNA mutational burden alone.

4.2.3.4.4 Transcriptional Analysis of Gene Expression Signatures in Whole Blood

Using RNA extracted from whole blood samples collected both prior to and following administration of pembrolizumab, messenger RNA transcript profiling may be performed to assess gene expression and evaluate whether changes in specific genes or sets of genes may represent a PD biomarker of response.

4.2.3.4.5 Additional Biomarker Analyses

Tumor and blood (including serum and plasma) samples may undergo proteomic, genomic, metabolomic, transcriptional, and other exploratory analyses, including the following:

Immunohistochemistry. In addition to tumor PD-L1 expression, the expression of other biomarkers may be evaluated using IHC.

Serum and Plasma analyses. Plasma and serum will be collected and frozen for future analyses. Assays to be performed may include measurement of sPD-L1 levels using an ELISA assay recently developed at Merck, protein profiling, miRNA profiling, exosome isolation and analysis, and circulating tumor DNA analysis. These analyses may identify novel serum/plasma biomarkers to aid in subject selection for pembrolizumab therapy.

Genetic Analysis of T cell Repertoire. Whole blood and tumor DNA may also be analyzed for T cell receptor utilization as an indicator of clonal expansion of T cells. The correlation between T cell clonality among TILs and peripheral blood T cells may be investigated. Expansion of TIL clones detected in the peripheral blood may represent a PD biomarker of pembrolizumab response.

4.2.3.4.6 Planned Genetic Analyses

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

4.2.3.5 Future Biomedical Research

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

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

4.3 Benefit/Risk

It cannot be guaranteed that subjects in clinical trials will directly benefit from treatment during participation, as clinical trials are designed to provide information about the safety and effectiveness of an investigational medicine.

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

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

Male and female subjects with any of the multiple advanced (metastatic and/or unresectable) solid tumors listed below with adequate tumor tissue for primary biomarker analysis and of at least 18 years of age will be enrolled in this trial.

5.1.2 Subject Inclusion Criteria

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

1. Be willing and able to provide written informed consent/assent for the trial. The subject may also provide consent/assent for Future Biomedical Research. However, the subject may participate in the main trial without participating in Future Biomedical Research.
2. Be ≥18 years of age on the day of signing informed consent.
3. Have a histologically or cytologically-documented, advanced (metastatic and/or unresectable) solid tumor that is incurable and for which prior standard first-line treatment has failed. Patients must have progressed on or be intolerant to therapies that are known to provide clinical benefit. There is no limit to the number of prior treatment regimens.

   Note: Prior neoadjuvant or adjuvant therapy included in initial treatment may not be considered first- or later-line SOC treatment unless such treatments were completed less than 12 months prior to the current tumor recurrence.
4. Have one of the following advanced (unresectable and/or metastatic) tumor types:
   - (A) Anal Squamous Cell Carcinoma,
   - (B) Biliary Adenocarcinoma (gallbladder or biliary tree (intrahepatic or extrahepatic cholangiocarcinoma) except Ampulla of Vater Cancers,
   - (C) Neuroendocrine Tumors (well- and moderately-differentiated), of the lung, appendix, small intestine, colon, rectum, or pancreas,
   - (D) Endometrial Carcinoma (sarcomas and mesenchymal tumors are excluded),
   - (E) Cervical Squamous Cell Carcinoma,
   - (F) Vulvar Squamous Cell Carcinoma,
   - (G) Small Cell Lung Carcinoma,
   - (H) Mesothelioma (Malignant Pleural Mesothelioma),
   - (I) Thyroid Carcinoma (Papillary or Follicular Subtypes),
   - (J) Salivary Gland Carcinoma (sarcomas and mesenchymal tumors are excluded)

OR

(K) Any advanced solid tumor (except CRC), which is MSI-H.

Note: FOLLOWING ENROLLMENT OF THE INITIAL APPROXIMATELY 100 SUBJECTS IN THIS COHORT, SUBSEQUENT ENROLLMENT WILL BE LIMITED SUCH THAT A TOTAL OF NO MORE THAN APPROXIMATELY 20 SUBJECTS WITH ANY SINGLE SPECIFIC TUMOR TYPE ARE ENROLLED IN THIS MSI-H CANCER COHORT. THE IVRS SYSTEM WILL BE USED TO DETERMINE IF SUBJECTS WITH AN MSI-H TUMOR OF A PARTICULAR TYPE MAY BE ENROLLED.

5. Have submitted an evaluable tissue sample for biomarker analysis from a tumor lesion not previously irradiated (exceptions may be considered after consultation with and approval by the Sponsor) (See Procedure Manual for detailed instructions). The tumor tissue submitted for analysis must be from a single tumor tissue specimen and of sufficient quantity and quality to allow assessment of ALL required primary biomarkers.

   Note: SUBJECTS WILL NOT BE ELIGIBLE TO ENROLL INTO GROUPS A-J UNLESS ALL THREE PRIMARY BIOMARKERS (TUMOR PD-L1 EXPRESSION, GEP SCORE, and MSI-H STATUS) CAN BE ASSESSED USING TISSUE FROM THE SAME SINGLE TUMOR SPECIMEN.

   Note: FOLLOWING ENROLLMENT OF THE INITIAL APPROXIMATELY 100 SUBJECTS WITH MSI-H CANCER IN GROUP K, ADDITIONAL SUBJECTS WILL NOT BE ELIGIBLE TO ENROLL INTO GROUP K UNLESS TISSUE FROM THE SAME SINGLE TUMOR SPECIMEN USED FOR PRIOR MSI TESTING IS SUBMITTED FOR SUBSEQUENT RETROSPECTIVE MSI TESTING.

6. If enrollment in Groups A-J has moved to biomarker enrichment, have a tumor that is positive for one or more of the pre-specified primary biomarker(s), as assessed by the central laboratory. These enrichment biomarkers may be PD-L1 expression by IHC (at a percentage to be prespecified), a positive tumor RNA GEP score (at a prespecified cut-off), and/or tumor MSI-H.

7. Have radiologically measurable disease based on RECIST 1.1. Independent central radiologic review must confirm the presence of radiologically measureable disease based on RECIST 1.1 for the subject to be eligible to participate in the trial (see Site Imaging Manual for detailed instructions). 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. This performance status must be confirmed within 3 days prior to the first dose of pembrolizumab or the subject must be excluded.

9. Life expectancy of at least 3 months.

10. Demonstrate adequate organ function as defined in Table 6.

Table 6 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1,500/mcL
Platelets	≥100,000/mcL
Hemoglobin (Hgb)	≥9.0 g/dL or ≥5.6 mmol/L, without recent transfusion (defined as a transfusion that has occurred within 2 weeks of the Hgb measurement)
Renal	
Creatinine **OR** Measured or calculated[a] creatinine clearance (GFR can also be used in place of creatinine or creatinine clearance)	≤1.5xULN **OR** ≥60.0 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 should be calculated per institutional standard.	

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

12. Female subjects of childbearing potential (See Section 5.7.2) must be willing to use an adequate method of contraception, as outlined in Section 5.7.2. – Contraception, for the course of the study through 120 days after the last dose of trial medication.

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

13. Male subjects of childbearing potential (See Section 5.7.2.) must agree to use an adequate method of contraception, as outlined in Section 5.7.2. – Contraception, for the course of the study through 120 days after the last dose of trial medication.

Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception method 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.
3. Has an active autoimmune disease that has required systemic treatment in the 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) or treatment with drugs (e.g. neomercazol, carbamazole, etc.) that function to decrease the generation of thyroid hormone by a hyperfunctioning thyroid gland (e.g in Graves' disease) is not considered a form of systemic treatment of an autoimmune disease.
4. Has had a prior anti-cancer monoclonal antibody (mAb) within 4 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from an AE due to mAbs administered more than 4 weeks earlier.
5. 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 an AE 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 trial.

   Note: If a subject has undergone major surgery, that subject must have recovered adequately from any toxicity and/or complications from this procedure prior to starting therapy.
6. Has a known additional malignancy within 2 years prior to enrollment with the exception of curatively treated basal cell carcinoma of the skin, squamous cell carcinoma of the skin, and/or curatively resected *in situ* cancers.

   Note: For subjects with documented Lynch Syndrome, or other genetic defects in DNA repair, and an additional malignancy within 2 years prior to enrollment, an exception to this exclusion criterion may be granted based on consultation with and approval by the Sponsor.
7. Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided these brain metastases are stable (without evidence of progression by

imaging over a period of at least 4 weeks and any neurologic symptoms have returned to baseline), they have no evidence of new or enlarging brain metastases (confirmed by imaging within 28 days of the first dose of trial treatment), and they 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.

8. Has known glioblastoma multiforme of the brainstem.
9. Has a history of (non-infectious) pneumonitis that required steroids or current pneumonitis.
10. Has an active infection requiring systemic therapy.
11. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.
12. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.
13. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the screening visit through 120 days after the last dose of trial treatment.
14. Has previously participated in any other pembrolizumab (MK-3475) trial, or received prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, or any other immune-modulating mAb (including ipilimumab and any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways).
15. Has a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies). No HIV testing is required unless mandated by local health authority.
16. Has known active Hepatitis B (i.e. HBsAg positive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected). No testing for Hepatitis B and Hepatitis C is required unless mandated by local health authority.
17. Has received a live vaccine within 30 days of planned start of study therapy.

    Note: The killed virus vaccines used for seasonal influenza vaccines for injection are allowed; however, intranasal influenza vaccines (e.g., FluMist®) are live attenuated vaccines and are not allowed.
18. Has severe hypersensitivity (≥Grade 3) to pembrolizumab and/or any of its excipients.
19. Has a known history of active tuberculosis (TB, *Bacillus tuberculosis*).

5.2 Trial Treatment(s)

The treatment to be used is outlined below in Table 7.

Table 7 Trial Treatment

Drug	Dose/ Potency	Dose Regimen*	Route of Administration	Regimen/ Treatment Period	Use
Pembrolizumab (MK-3475)	200 mg	Q3W	IV	Day 1 of each 3 week cycle	Experimental
*Pembrolizumab (MK-3475) doses may be withheld due to toxicity as described in Section 5.2.1.2.					

Trial treatment should begin on the day of allocation but up to 3 days after allocation is permitted.

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

5.2.1 Dose Selection/Modification

5.2.1.1 Dose Selection (Preparation)

The rationale for selection of the fixed 200 mg IV Q3W pembrolizumab dose to be used in this trial is provided in Section 4.2.2. Details on preparation and administration of pembrolizumab are provided in the Pharmacy Manual.

5.2.1.2 Dose Modification

Adverse events associated with pembrolizumab exposure may represent an immunologic etiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of treatment. 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 8.

Table 8 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 treatment should be initiated first followed by oral steroid therapy. 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 (i.e. diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (i.e. 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		

AST / ALT elevation or Increased Bilirubin	Grade 2	Withhold	• Administer corticosteroids (initial dose of 0.5- 1mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable
	Grade 3 or 4	Permanently discontinue	• Administer corticosteroids (initial dose of 1-2mg/kg prednisone or equivalent) followed by taper	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold	• Initiate insulin replacement therapy for 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[1]		
Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (e.g. propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or Permanently discontinue[1]		
Hypothyroidism	Grade 2-4	Continue	• Initiate thyroid replacement hormones (e.g. levothyroxine or liothyroinine) per standard of care	• Monitor for signs and symptoms of thyroid disorders.
Nephritis and renal dysfunction	Grade 2	Withhold	• Administer corticosteroids (prednisone 1-2mg/kg or equivalent) followed by taper.	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
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		
1. Withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician. **NOTE:** For subjects with Grade 3 or 4 immune-related endocrinopathy where withholding of pembrolizumab is required, pembrolizumab may be resumed when AE resolves to ≤ Grade 2 and is controlled with hormonal replacement therapy or metabolic control has been achieved (in case of T1DM).				

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

Pembrolizumab may cause severe or life threatening infusion-reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab associated infusion reaction are provided in Table 9.

Table 9 Pembrolizumab Infusion Reaction Dose Modification and Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g. from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab 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 Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. **Subject is permanently discontinued from further study drug treatment.**	No subsequent dosing
Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE) at http://ctep.cancer.gov		

Other allowed dose interruptions for pembrolizumab

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

5.2.2 Timing of Dose Administration

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

Trial treatment of pembrolizumab may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons. Cycle 1 may be administered up to 3 days after the scheduled Day 1.

All trial treatments will be administered on an outpatient basis.

Pembrolizumab 200 mg will be administered as a 30 minute IV infusion every 3 weeks. 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). Refer to the Pharmacy Manual for specific instructions for the preparation of the pembrolizumab infusion fluid and administration of infusion solution.

5.2.3 Trial Blinding/Masking

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

Imaging data for the primary analysis will be centrally reviewed by independent radiologist(s) without knowledge of subject-level primary biomarker status.

5.3 Randomization or Treatment Allocation

Treatment allocation/randomization will occur centrally using an interactive voice response system / integrated web response system (IVRS/IWRS). There is one treatment arm. Subjects participating in this trial will be assigned to pembrolizumab 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 medications will be recorded on the case report form (CRF) including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date should also be included on the CRF.

All concomitant medications received within 28 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered more than 30 days after the last dose of trial treatment should be recorded for SAE and ECI monitoring as defined in Section 7.2.

5.5.2 Prohibited Concomitant Medications

Subjects are prohibited from receiving the following therapies during Screening, as specified in the Exclusion Criteria (Section 5.1.3), and during the Treatment Phase of this trial (including during retreatment for relapse):

- Antineoplastic systemic chemotherapy or biological therapy

- Immunotherapy not specified in this protocol

  Note: Even if used for the treatment of medical conditions not considered to be of an immune etiology, agents that target receptors expressed on immune cells (e.g. denosumab) are prohibited.

- Chemotherapy not specified in this protocol

  Note: For patients receiving hormonal blockade for the treatment of an additional malignancy or as cancer chemoprevention, an exception to this prohibition may be granted based on consultation with and approval by the Sponsor.

- Investigational agents other than pembrolizumab (MK-3475)

- Radiation therapy

  Note: Radiation therapy to a symptomatic lesion or to the brain may be considered on a case-by-case basis after consultation with and approval by the Sponsor. Such a radiated lesion must not be a RECIST 1.1 target lesion and the subject must have clear measurable disease outside the irradiated field.

- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella, zoster, yellow fever, intranasal influenza, rabies, BCG, and typhoid vaccine.

  - UK Subjects only: Live vaccines within 30 days prior to the first dose of trial treatment, while participating in the trial, and for 120 days after the last dose of trial treatment.

- Glucocorticoids (inhaled steroids as part of a stable regimen for the treatment of asthma/COPD are permitted) for any purpose other than to modulate AEs of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.

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 describe other medications which are prohibited in this trial.

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

5.6 Rescue Medications & Supportive Care

5.6.1 Supportive Care Guidelines for Pembrolizumab

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined along with the dose modification guidelines in Section 5.2.1.2, Table 8. Where appropriate, these guidelines include the use of oral or

intravenous treatment with corticosteroids as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each AE, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab.

Note: If after evaluation, the event is determined to be not related to pembrolizumab treatment, the investigator does not need to follow the treatment guidance (as outlined below). Refer to Table 8 in Section 5.2.1.2 for guidelines regarding dose modification and supportive care.

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

5.7 Diet/Activity/Other Considerations

5.7.1 Diet

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

5.7.2 Contraception

Pembrolizumab may have adverse effects on a fetus *in utero*. Furthermore, it is not known if pembrolizumab has transient adverse effects on the composition of sperm.

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 either:

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

OR

(2) have had a hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy or bilateral tubal ligation/occlusion, at least 6 weeks prior to screening;

OR

(3) have a congenital or 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 study drug and for 120 days after the last dose of study drug by complying with one of the following:

(1) practice abstinence† from heterosexual activity;

OR

(2) use (or have their partner use) acceptable contraception during 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 ERCs/IRBs. Periodic abstinence (e.g., calendar, ovulation, sympto-thermal, post-ovulation methods, etc.) and withdrawal are not acceptable methods of contraception.

Acceptable methods of contraception are as follows‡:

Single method (one 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 two 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 subjects of childbearing potential must adhere to the contraception requirement (described above) from the day of study medication initiation (or 14 days prior to the initiation of study medication for subjects utilizing oral contraception) throughout the study period up to 120 days after the last dose of trial therapy. If there is any question that a subject of childbearing potential will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

5.7.3 Use in Pregnancy

If a subject inadvertently becomes pregnant while on treatment with pembrolizumab, the subject will immediately be removed from the trial. 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 trial 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 trial 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

5.8.1 Discontinuation of Treatment

Discontinuation of treatment does not represent withdrawal from the trial.

As certain data on clinical events beyond treatment discontinuation may be/are important to the study, they must be collected through the subject's last scheduled follow-up, even if the subject has discontinued treatment. Therefore, all subjects who discontinue trial treatment prior to completion of the treatment will still continue to participate in the trial as specified in Section 6.0 - Trial Flow Chart and Section 7.1.8.1 – Other Procedures Withdrawal/Discontinuation.

Subjects may discontinue treatment at any time for any reason or be dropped from treatment/vaccination at the discretion of the investigator should any untoward effect occur. In addition, a subject may be discontinued from treatment by the investigator or the Sponsor if treatment is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding procedures to be performed at treatment discontinuation are provided in Section 7.1.8 – Other Procedures.

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

- The subject or subject's legally acceptable representative requests to discontinue treatment.
- Radiologic disease progression is confirmed by local site assessment.

  Note: Subjects should be managed by irRECIST, with PD confirmed as outlined in Section 5.8.1.

  Note: Exception if Sponsor approves treatment continuation (Section 7.1.4.7.1).
- Unacceptable adverse experiences as described in Section 5.2.1.2
- Intercurrent illness that prevents further administration of treatment
- Investigator decides to withdraw the subject.
- Any progression or recurrence of any malignancy, or any occurrence of another

malignancy that requires active treatment

- Recurrent Grade 2 pneumonitis
- The subject has a confirmed positive serum pregnancy test.
- Noncompliance with trial treatment or procedure requirements
- The subject is lost to follow-up.
- Discontinuation of treatment may be considered for subjects who have attained a confirmed complete response (CR) and have been treated for at least 8 cycles (at least 24 weeks), receiving at least 2 doses of pembrolizumab and at least 80% of the planned dose beyond the date when the initial CR was declared. Subjects who stop trial treatment with stable disease (SD), partial response (PR), or CR, may be eligible for up to 1 year (17 cycles) of pembrolizumab if they experience disease progression after stopping pembrolizumab. This retreatment is termed the Second Course Phase (Retreatment) and is described in detail in Section 7.1.9.2.1.

- The subject has completed 35 administrations of pembrolizumab (approximately 2 years of treatment).

  Note: The number of treatments is calculated starting with the first dose. Subjects who discontinue pembrolizumab after 35 administrations may be eligible for up to 17 administrations (approximately one year) of additional study treatment if they progress after discontinuing study treatment provided they meet additional criteria detailed in Section 7.1.9.2.1. The decision to retreat will be at the discretion of the investigator, provided that such a subject meets the criteria for treatment and the trial is ongoing (see Section 7.1.9.2.1).

The End of Treatment and Follow-up visit procedures are listed in Section 6 (Protocol Flow Chart) and Section 7.1.9 (Visit Requirements). After the end of treatment, each subject will be followed for 30 days for AE and ECI monitoring and for 90 days for SAE monitoring, as described in Section 7.2. Subjects who discontinue for reasons other than PD will have post-treatment follow-up for disease status until disease progression, initiating a non-study cancer treatment, withdrawing consent or becoming lost to follow-up. After documented disease progression each subject will be followed by telephone for OS until death, withdrawal of consent, or the end of the trial, whichever occurs first.

For subjects who are discontinued from treatment but continue to be monitored in the trial, all visits and procedures, as outlined in the trial flowchart, should be completed.

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

Discontinuation from treatment is “permanent.” Once a subject is discontinued, he/she shall not be allowed to restart treatment.

5.8.2 Withdrawal from the Trial

A subject must be withdrawn from the trial if the subject or subject's legally acceptable representative withdraws consent from the trial.

If a subject withdraws from the trial, they will no longer receive treatment or be followed at scheduled protocol visits.

Specific details regarding procedures to be performed at the time of withdrawal from the trial including the procedures to be performed should a subject repeatedly fail to return for scheduled visits and/or if the study site is unable to contact the subject, as well as specific details regarding withdrawal from Future Biomedical Research are outlined in Section 7.1.8 – Other Procedures.

5.8.3 Treatment After Initial Radiologic Progression (irRECIST-based Management)

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 apparent increase in tumor burden (i.e., pseudoprogression) or even the appearance of new lesions. Standard RECIST-based assessment of disease progression may, thus, not provide an accurate assessment of response to immunotherapeutic agents such as pembrolizumab. For this reason, irRECIST has been developed to help guide treatment decisions during tumor immunotherapy.

For subjects who have initial radiological evidence of radiological PD by RECIST 1.1 as determined by the site, the investigator may elect to continue a subject on study treatment until repeat imaging is obtained (irRECIST-based management) (see Table 10). This clinical judgment decision by the investigator should only be made if the subject is clinically stable, based on clinical factors including performance status, clinical symptoms, and laboratory data. Such subjects may continue to receive study treatment and a imaging-based tumor assessment should be repeated ≥ 4 weeks later in order to reassess PD per investigator assessment.

Clinical stability is defined by the following:

- Absence of signs and symptoms of clinically significant progression of disease, including worsening of laboratory values
- No decline in ECOG performance status
- Absence of rapid progression of disease
- Absence of tumor progression at critical anatomical sites that requires urgent alternative medical intervention (e.g., CNS metastasis with potential for cord compression)

NOTE: Subjects exhibiting toxicity from trial therapy as outlined in Section 5.2.1.2 and 7.2 may NOT continue to receive trial therapy.

NOTE: Any subject deemed **clinically unstable** should be discontinued from trial treatment at investigator-assessed 1st radiologic evidence of PD and is not required to have repeat imaging for PD confirmation.

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

Upon repeat imaging, PD will be confirmed if ANY of the following occur by irRECIST:

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

If repeat imaging confirms PD due to any of the scenarios listed above, subjects will be discontinued from trial therapy (exception noted below in Section 7.1.4.7.1).

Upon repeat imaging, PD will have failed to be confirmed if ALL of the following occur by irRECIST:

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

If repeat local site imaging fails to confirm PD by irRECIST and the subject continues to be clinically stable, treatment may continue and follow the regular imaging schedule.

When feasible, subjects should not be discontinued until PD is confirmed by the local site investigator radiology assessment. This allowance to continue treatment despite initial radiologic PD takes into account the observation that some subjects can have a transient tumor flare in the first few months after the start of immunotherapy, and then experience subsequent disease response. Subjects who are deemed clinically unstable are not required to have repeat tumor imaging for confirmation of PD. Tumor flares include any of the following scenarios:

- Worsening of existing target lesion(s)
- Worsening of existing non-target lesion(s)

- Development of new lesion(s)

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

Table 10 Imaging and Treatment After First Radiologic Evidence of PD (irRESIST-based Management)

	Clinically Stable		Clinically Unstable	
	Imaging	**Treatment**	**Imaging**	**Treatment**
1st radiologic evidence of PD by RECIST 1.1	Repeat imaging at ≥ 4 weeks at site to confirm PD	May continue study treatment at the local site investigator's discretion while awaiting confirmatory tumor imaging by site by irRECIST.	Repeat imaging at ≥ 4 weeks to confirm PD per physician discretion only	Discontinue treatment
Repeat tumor imaging confirms PD by irRECIST at the local site	No additional imaging required	Discontinue treatment (exception is possible upon consultation with and approval by Sponsor)	No additional imaging required	N/A
Repeat tumor imaging shows SD, PR or CR by irRECIST at the local site	Continue regularly scheduled imaging assessments	Continue study treatment at the local site investigator's discretion	Continue regularly scheduled imaging assessments	May restart study treatment if condition has improved and/or clinically stable per investigator's discretion. Next tumor image should occur according to the regular imaging schedule outlined in the protocol

5.8.4 Discontinuation of Study Therapy After Complete Response

Discontinuation of treatment may be considered for subjects who have attained a confirmed CR and who have been treated with at least 8 administrations of pembrolizumab and who have received at least two administrations of pembrolizumab beyond the date when the initial CR was declared. Subjects who then experience radiologic investigator-confirmed disease progression may be eligible for up to 17 administrations (approximately one year) of additional treatment with pembrolizumab at the discretion of the investigator if no cancer treatment has been administered since the last dose of pembrolizumab, the subject meets the Inclusion/Exclusion criteria, and the trial remains open. Subjects will resume therapy at the same dose and schedule utilized at the time of initial discontinuation. Additional details are provided in Section 7.1.9.2.1.

5.9 Subject Replacement Strategy

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

5.10 Beginning and End of the Trial

The overall trial begins when the first subject signs the informed consent form. The overall trial ends when the last subject is at least 6 months post their last study medication administration, discontinues from the trial or is lost to follow-up (i.e. the subject is unable to be contacted by the investigator).

5.11 Clinical Criteria for Early Trial Termination

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

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

In the event the Sponsor decides 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 Initial Treatment Phase Flowchart

Details regarding the procedures listed in this table are outlined in Section 7.

Trial Period:	Screening Phase				Treatment Cycles (3-Week Cycles)						End of Treatment	Post-Treatment		
Treatment Cycle/Title:	Screening (Visit 1)				1	2	3	4	To be repeated beyond 6 cycles 5	6	Discon	Safety Follow-up	Follow Up Visits	Survival Follow-up[a]
Scheduling Window (Days)[b]	-42 to -1	-28 to -1	-10 to -1	-3 to -1	+3	± 3	± 3	± 3	± 3	± 3	At time of discon	30 days post last dose (± 7 days)	Every 12 weeks post discon (±7 days)	Every 12 weeks (±7 days)
Administrative Procedures														
Informed Consent	X[c]													
Informed Consent for Future Biomedical Research (FBR)	X													
Inclusion/Exclusion Criteria		X												
Subject Identification Card	X													
Demographics and Medical History		X												
Prior and Concomitant Medication Review		X	X		X	X	X	X	X	X	X	X		
Prior Cancer Treatment Details		X												
Obtain screening number	X													
Obtain treatment/allocation number and study drug assignment using IVRS/IWRS					X									
Pembrolizumab administration					X	X	X	X	X	X				
Post-study Anticancer Therapy Status													X	X

Trial Period:	**Screening Phase**				**Treatment Cycles (3-Week Cycles)**						**End of Treatment**	**Post-Treatment**		
Treatment Cycle/Title:	**Screening (Visit 1)**				**1**	**2**	**3**	**4**	**To be repeated beyond 6 cycles** 5	**6**	**Discon**	**Safety Follow-up**	**Follow Up Visits**	**Survival Follow-up[a]**
Scheduling Window (Days)[b]	**-42 to -1**	**-28 to -1**	**-10 to -1**	**-3 to -1**	**+3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At time of discon**	**30 days post last dose (± 7 days)**	**Every 12 weeks post discon (±7 days)**	**Every 12 weeks (±7 days)**
Survival Status[a]					<- ->									**X**
Clinical Procedures/Assessments														
AE Monitoring		**X**			**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
12-Lead Electrocardiogram (Locally performed)		**X**			**As clinically indicated**									
Full Physical Examination		**X**									**X**			
Directed Physical Examination					**X**	**X**	**X**	**X**	**X**	**X**				
Vital Signs (and Weight and Height)[d]		**X**			**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
ECOG Performance Status				**X[e]**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
Laboratory Procedures/Assessments: analysis performed by LOCAL laboratory														
Pregnancy Test – Urine or Serum β-HCG[f]			**X[e]**											
PT/INR and aPTT[g]			**X[e]**											
CBC with Differential[g]			**X[e]**			**X**	**X**	**X**	**X**	**X**	**X**	**X**		
Chemistry Panel[g]			**X[e]**			**X**	**X**	**X**	**X**	**X**	**X**	**X**		
Urinalysis[g]			**X[e]**			**X**		**X**		**X[h]**		**X**		
T3 or FT3, FT4 and TSH[g]			**X[e]**			**X**		**X**		**X[h]**		**X**		

Trial Period:	Screening Phase				Treatment Cycles (3-Week Cycles)						End of Treatment	Post-Treatment		
Treatment Cycle/Title:	Screening (Visit 1)				1	2	3	4	To be repeated beyond 6 cycles 5	6	Discon	Safety Follow-up	Follow Up Visits	Survival Follow-up[a]
Scheduling Window (Days)[b]	-42 to -1	-28 to -1	-10 to -1	-3 to -1	+3	± 3	± 3	± 3	± 3	± 3	At time of discon	30 days post last dose (± 7 days)	Every 12 weeks post discon (±7 days)	Every 12 weeks (±7 days)
Laboratory Procedures/Assessments: analysis performed by CENTRAL laboratory														
Whole Blood Sample for MSI DNA[i]	X													
Pharmacokinetics [j]					X			X						
Correlative Blood Samples (DNA and RNA)[k]					X	X	X				X			
Blood Samples for Biomarkers (Plasma, Serum)[k]					X									
Blood Sample for Genetics[l]					X									
Efficacy Measurements														
Tumor Imaging and RECIST Assessment [m]		X					X[n]			X[n]	X[o]		X[p]	
Additional Imaging														
Brain Imaging (for subjects with known brain metastases at baseline,[q] and those with either small cell lung or thyroid cancers[s])		X			X (at time of radiologic CR)[r]									
Imaging for Bone Metastases[t]		X												

Trial Period:	Screening Phase				Treatment Cycles (3-Week Cycles)						End of Treatment	Post-Treatment		
Treatment Cycle/Title:	Screening (Visit 1)				1	2	3	4	To be repeated beyond 6 cycles 5	6	Discon	Safety Follow-up	Follow Up Visits	Survival Follow-up[a]
Scheduling Window (Days)[b]	-42 to -1	-28 to -1	-10 to -1	-3 to -1	+3	± 3	± 3	± 3	± 3	± 3	At time of discon	30 days post last dose (± 7 days)	Every 12 weeks post discon (±7 days)	Every 12 weeks (±7 days)
Tumor Tissue Analysis[c]														
Tumor tissue submitted for biomarker analysis[u, i]	X													
Optional submission of other archival tumor tissue specimen(s) for biomarker analysis[v]					X[v]									
Patient Reported Outcomes														
EuroQol EQ-5D[w]					X	X	X	X			X	X		
EORTC QLQ-C30[w]					X	X	X	X			X	X		

a. After documented local site assessed disease progression, or the start of new anti-cancer treatment; contacts are approximately every 12 weeks by telephone. Updated survival status may be requested by the Sponsor during the course of the study. Upon Sponsor notification, all participants who do not/will not have a scheduled study visit or study contact during the Sponsor defined time period will be contacted for their survival status (excluding participants that have a death event previously recorded).
b. In general, assessments/procedures are to be performed on Day 1 and prior to the dose of treatment for each cycle unless otherwise specified.
c. Informed consent must be obtained prior to sending any tumor tissue specimens to the study central laboratory for biomarker assessment. Subjects who do not have an available tumor tissue specimen must sign the study consent prior to undergoing any new biopsy procedure to collect such tissue. Such a procedure should not be performed if it is not otherwise clinically indicated and would create significant risk for the subject (including (but not limited to) biopsies of the brain, lung/mediastinum, pancreas, or endoscopic procedures extending beyond the esophagus, stomach or bowel). ICF should be performed within 42 days of Day 1. MSI testing must be done for all Group K subjects, prior to study enrollment.
d. Height will be measured at visit 1 only.
e. ECOG for screening is to be performed within 3 days of the first dose. The laboratory tests for screening are to be performed within 10 days prior to the first dose of pembrolizumab.
f. 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. Monthly pregnancy testing (serum and/or urine tests) should be conducted as per local regulations where applicable. Monthly pregnancy testing is required for United Kingdom subjects, as stipulated by Clinical Trials Facilitation Group (CTFG) guidance.
g. After Cycle 1, laboratory samples can be collected up to 3 days prior to Day 1 of each cycle.
h. To be repeated every 2 cycles after Cycle 6.
i. Collection of whole blood into an EDTA tube for DNA extraction for MSI testing must occur sometime during the Screening period.
j. PK pre-dose (trough) samples will be collected within 24 hours before infusion at Cycles 1 and 4. Post dose sample will be collected at Cycle 1 within 30 minutes after completion of infusion.
k. Blood samples for correlative studies (for DNA and RNA) should be collected at Cycle 1, Day 1- **Pre-dose**, Cycle 2 Day 1- **Pre-dose**, Cycle 3 Day 1- **Pre-dose** and again at treatment discontinuation. Blood samples for serum and plasma for biomarker research are only collected at Cycle 1 Day 1- **Pre-dose**. See Procedures Manual.
l. This blood sample will be drawn for HLA genotyping and for planned analysis of the association between genetic variants in DNA and drug response. Data analysis will be limited to HLA genotyping if the IRB/IEC does not approve of, or if there is a documented law or regulation prohibiting, the planned analysis of the association between DNA variations and drug response. Remaining extracted DNA will be stored for future biomedical research if the subject signs the FBR consent.

m. The initial tumor imaging will be performed after tissue collection and within 28 days prior to the date of Cycle 1 Day 1. The central imaging vendor will confirm presence of measurable disease. The processes for image collection and transmission to the central vendor are in the Site Imaging Manual.
n. The first on-study imaging time point will be performed at 9 weeks (63 ±7 days) after the date of Cycle 1 Day 1, and then every 9 weeks (63 ± 7 days) thereafter, or more frequently if clinically indicated. After 12 months, imaging frequency should be reduced to every 12 weeks (84 ±7 days). Imaging timing should follow calendar days and should not be adjusted for delays in cycle starts (i.e., administration of pembrolizumab). Local site investigator assessments will be used for subject management. The processes for image collection and transmission to the central vendor are in the Site Imaging Manual.
o. In subjects who discontinue study therapy without local site confirmed disease progression, a radiologic evaluation should be performed at the time of treatment discontinuation (i.e., date of discontinuation ± 4 week window). If a previous scan was obtained within 4 weeks prior to the date of discontinuation, then a scan at treatment discontinuation is not mandatory.
p. In subjects who discontinue study therapy without documented local site disease progression, every effort should be made to continue monitoring their disease status by radiologic imaging every 12 weeks (84 ± 7 days) in the first year and every 24 weeks (168 ± 7days) after year 1 until (1) the start of new anti-cancer treatment, (2) disease progression per local site assessment, (3) death, or (4) the end of the trial, whichever occurs first.
q. In order for subjects with previously treated brain metastases to be eligible to participate in the study, documented stability by brain imaging over a period of at least 4 weeks is required and there must be confirmation of no new or enlarging brain metastases within 28 days of the first dose of trial treatment.
r. For any subject with known brain metastases at baseline, and who achieves a CR during trial treatment, a follow-up brain scan is required for confirmatory assessment of CR.
s. For subjects with either small cell lung or thyroid cancers (and without a history of stable brain metastases), the absence of brain metastases must be locally confirmed by brain scan. Central confirmation of the absence of brain metastases is not required.
t. For any subject with an elevated baseline serum alkaline phosphatase level (>1.5x upper limit of normal range), bone imaging (e.g. bone scan or PET scan) should be conducted to identify possible bone metastases. If new bone metastases are identified, then additional baseline and all subsequent tumor imaging studies should include such lesions in the imaging field.
u. Tumor tissue for biomarker analysis must be submitted (for all subjects in Groups A-J). Adequacy of the submitted tumor specimen for required biomarker analyses must be confirmed by the central laboratory before enrollment. For the initial approximately 100 subjects in group K, if available, tissue should be submitted, but this is not required. For subsequent Group K subjects, tissue must be submitted. Detailed instructions for tissue collection, process and shipment are provided in the Procedures Manual. If the subject signs the FBR consent, any remaining tissue that would ordinarily be discarded at the end of the main study will be retained for FBR.
v. Other archival specimens include any tumor tissue samples collected at dates other than the date of collection of the tumor sample submitted for primary biomarker assessment. If the patient has received more than one prior therapy, more than one archival tumor specimen may be submitted, corresponding to different stages in prior treatment (i.e., baseline prior to any treatment and after each subsequent therapy prior to the most recent therapy. These optional archival tumor tissue specimens should be submitted at or after study start (Cycle 1 Day 1).
w. Patient reported outcomes (PROs) are assessed at every cycle for the first 4 cycles, then every 3 cycles until 9 months, then every 4 cycles until PD while the subject is receiving study treatment, at the Treatment Discontinuation Visit, and at the 30-day Safety Follow-up Visit (The visit schedule should be Cycle 1, 2, 3, 4, 7, 10, 14, 18, 22, etc.). If the Treatment Discontinuation Visit occurs 30 days after the last dose of study treatment, at the time of the mandatory Safety Follow up Visit, PROs need not be repeated. The PROs should be administered in the following order: EQ-5D followed by EORTC QLQ-C30.

6.2 Second Course Phase (Retreatment) Flowchart

Trial Period:	Treatment Cycles (3-Week Cycles)						End of Treatment	Post-Treatment		
					To be repeated beyond 6 cycles					
Treatment Cycle/Title:	1	2	3	4	5	6	Discon	Safety Follow-up	Follow Up Visits	Survival Follow-up[a]
Scheduling Window (Days)[b]:	+3	± 3	± 3	± 3	± 3	± 3	At time of discon	30 days post last dose (± 7 days)	Every 12 weeks post discon (±7 days)	Every 12 weeks (±7 days)
Administrative Procedures										
Inclusion/Exclusion Criteria	X									
Prior and Concomitant Medication Review	X	X	X	X	X	X	X	X		
Post-study Anticancer Therapy Status									X	X
Pembrolizumab (MK-3475) Administration	X	X	X	X	X	X				
Survival Status[a]	←---→									X
Clinical Procedures/Assessments										
AE Monitoring	X	X	X	X	X	X	X	X	X	
Full Physical Examination	X						X			
Directed Physical Examination		X	X	X	X	X				
Vital Signs	X[c]	X	X	X	X	X	X			
ECOG Performance Status	X[d]	X	X	X	X	X	X			
Tumor Tissue Collection										
Optional Biopsy Recurrent Tumor	X									
Laboratory Procedures/Assessments: analysis performed by LOCAL laboratory										
Pregnancy Test – Serum or Urine[e]	X									
CBC with Differential[f]	X[d]	X	X	X	X	X	X	X		
Chemistry Panel[f]	X[d]	X	X	X	X	X	X	X		

Trial Period:	Treatment Cycles (3-Week Cycles)						End of Treatment	Post-Treatment		
					To be repeated beyond 6 cycles					
Treatment Cycle/Title:	1	2	3	4	5	6	Discon	Safety Follow-up	Follow Up Visits	Survival Follow-up[a]
Scheduling Window (Days)[b]:	+3	± 3	± 3	± 3	± 3	± 3	At time of discon	30 days post last dose (± 7 days)	Every 12 weeks post discon (±7 days)	Every 12 weeks (±7 days)
Urinalysis[f]	X[d]	X		X		X[g]		X		
T3 or FT3, FT4, and TSH[f]	X[d]	X		X		X[g]		X		
Laboratory Procedures/Assessments: analysis performed by CENTRAL laboratory										
Correlative Blood Samples (DNA and RNA)[h]	X	X	X				X			
Efficacy Measurements										
Tumor Imaging	X[i]		X[i]			X[i]	X[j]		X	

a. After documented local site assessed disease progression, or the start of new anti-cancer treatment; contacts are approximately every 12 weeks by telephone. Updated survival status may be requested by the Sponsor during the course of the study. Upon Sponsor notification, all participants who do not/will not have a scheduled study visit or study contact during the Sponsor defined time period will be contacted for their survival status (excluding participants that have a death event previously recorded).
b. In general, the window for each visit is ± 3 days unless otherwise noted.
c. Height will be measured at visit 1 only.
d. ECOG for screening is to be performed within 3 days of the first retreatment dose. The laboratory tests for screening are to be performed within 10 days prior to the first retreatment dose of pembrolizumab
e. For women of reproductive potential, a serum pregnancy test should be performed within 72 hours prior to first dose of trial treatment and repeated if required by local guidelines. A urine test can be considered if serum is not appropriate. Monthly pregnancy testing should be conducted as per local regulations where applicable. Monthly pregnancy testing is required for United Kingdom subjects, as stipulated by CTFG guidance
f. After Cycle 1, laboratory samples can be collected up to 3 days prior to Day 1 of each cycle.
g. To be repeated every 2 cycles after Cycle 6.
h. Whole blood sample for correlative studies (DNA and RNA) should be collected at Cycle 1, Day 1- **Pre-dose**, Cycle 2 Day 1- **Pre-dose**, Cycle 3 Day 1- **Pre-dose** and again at treatment discontinuation. See Procedures Manual.
i. The initial tumor imaging should be completed within 28 days prior to restarting treatment with pembrolizumab. The next imaging time point will be performed at 9 weeks (±7 days) after the first dose of the second course, and then every 9 weeks (63 ± 7 days) thereafter, or more frequently if clinically indicated. After 12 months, imaging frequency should be reduced to every 12 weeks (84 ±7 days). Imaging timing should follow calendar days and should not be adjusted for delays in cycle starts (i.e., administration of pembrolizumab). Local site investigator assessments will be used for subject management. The processes for image collection and transmission to the central vendor are in the Site Imaging Manual.
j. If a previous scan was obtained within 4 weeks prior to the date of discontinuation, then a scan at treatment discontinuation is not mandatory.

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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.

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

7.1.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee. Medical history will include all active conditions, and any condition diagnosed within the prior 10 years that are considered to be clinically significant by the investigator. Details regarding the cancer for which the subject has enrolled in the trial 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 medications taken by the subject within 28 days within the first dose of trial treatment. Treatment for the disease for which the subject has enrolled in the trial 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 medications, if any, taken by the subject during the trial through the Safety Follow-up visit. All medications related to reportable SAEs and ECIs should be recorded as defined in Section 7.2.

7.1.1.6 Prior Cancer Treatment Details

The investigator or qualified designee will review all prior cancer treatments including systemic treatments, prior transplantation, radiation, and surgeries and record these in the trial database.

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 treatment allocation. Each subject will be assigned only one screening number. Screening numbers must not be re-used for different subjects.

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

Specific details on screening visit requirements (screening/rescreening) are provided in Section 7.1.9.1.

7.1.1.8 Assignment of Treatment/Randomization Number

All eligible subjects will be allocated, by non-random assignment, and will receive an allocation number. The allocation number identifies the subject for all procedures occurring after treatment allocation. Once an allocation number is assigned to a subject, it can never be re-assigned to another subject. A single subject cannot be assigned more than 1 allocation number.

7.1.1.9 Pembrolizumab Administration

Trial Treatment: pembrolizumab (MK-3475) 200 mg IV Q3W (see Pharmacy Manual). In general, the window for each visit is ± 3 days unless otherwise noted. Cycle 1 treatment must be given within 3 days of allocation.

7.1.1.10 Post-Study Anticancer Therapy Status

The investigator or qualified designee will review all new antineoplastic therapy initiated after the last dose of trial treatment. If a subject initiates a new antineoplastic 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 antineoplastic therapy has been initiated the subject will move into survival follow-up.

7.1.1.11 Survival Status

After the start of new anti-cancer treatment or documented disease progression by the local site investigator using RECIST 1.1, the subject should be contacted by telephone as described in Section 7.1.9.3.3.

7.1.1.12 Trial Compliance (Medication)

Interruptions from the protocol specified treatment plan for 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 are provided in the Pharmacy Manual.

7.1.2 Clinical Procedures/Assessments

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

7.1.2.1 Adverse Event Monitoring

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

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

7.1.2.2 12-Lead Electrocardiogram

A standard 12-lead ECG will be performed locally using local standard procedures once during the screening period (see Section 6 – Trial Flow Chart) and then as clinically indicated. Clinically significant abnormal findings should be recorded as medical history.

7.1.2.3 Physical Exam

7.1.2.3.1 Full Physical Exam

The investigator or clinical designee will perform a complete physical exam during the screening period (See Trial Flow Chart Section 6.0). Clinically significant abnormal findings should be recorded as medical history. A full physical exam should be performed during screening and repeated at treatment discontinuation, as specified in the Study Flow Chart. After the first dose of trial treatment, new clinically significant abnormal findings should be recorded as AEs.

7.1.2.3.2 Directed Physical Exam

The investigator or qualified designee will perform a directed physical exam prior to dosing on Day 1 of each treatment cycle starting with Cycle 1, and at treatment discontinuation, as specified in the Trial Flow Chart. New clinically significant abnormal findings should be recorded as AEs.

7.1.2.4 Vital Signs

The investigator or qualified designee will obtain vital signs at screening, prior to dosing on Day 1 of each treatment cycle starting with Cycle 1, and at treatment discontinuation, as specified in the Trial Flow Chart. Vital signs should include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at screening only.

7.1.2.5 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status (see Section 12.5) at screening ≤3 days prior to dosing on Day 1 Cycle 1), on Day 1 of each treatment cycle and upon discontinuation of trial treatment, as specified in the Trial Flow Chart.

7.1.3 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below. The total amount of blood/tissue to be drawn/collected over the course of the trial (from pre-trial to post-trial visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per subject can be found in Appendix 12.8.

7.1.3.1 Laboratory Evaluations (Hematology, Chemistry and Urinalysis)

Laboratory tests to be performed during this study are specified in Table 11.

Table 11 Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Blood	Serum β-human chorionic gonadotropin (β-hCG)[a]
Hemoglobin	Alkaline phosphatase	Glucose	PT (INR) [d]
Platelet count	Alanine aminotransferase (ALT)	Protein	aPTT [d]
White Blood Cell (total and differential)	Aspartate aminotransferase (AST)	Specific gravity	Free triiodothyronine (FT3) (or Total T3)[e]
Red Blood Cell Count	Carbon dioxide (CO_2 or bicarbonate)[b]	Microscopic exam, if abnormal results are noted	Free thyroxine (T4)[e]
Absolute Neutrophil Count	Calcium	Urine pregnancy test[a]	Thyroid Stimulating Hormone (TSH)
Absolute Lymphocyte Count	Chloride		Pharmacokinetics
	Creatinine[c]		Blood for correlative studies
	Glucose		Biomarker Samples (Plasma, Serum)
	Phosphorus		Blood for Genetics (includes HLA Typing)
	Potassium		
	Sodium		
	Total Bilirubin		
	Direct Bilirubin, if total bilirubin is elevated above the upper limit of normal		
	Total protein		
	Blood Urea Nitrogen/Blood Urea		
	Uric acid		

[a] Perform on women of childbearing potential only. Urine pregnancy test is preferred. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. Monthly pregnancy testing is required for UK subjects, as stipulated by CTFG guidance.
[b] If these tests are not done as part of standard of care in a geographical region then these tests do not need to be performed.
[c] For subjects with a baseline calculated creatinine clearance below the normal institutional laboratory range, a baseline measured creatinine clearance should be performed.
[d] Coagulation factors (PT/INR and aPTT) should be tested as part of the screening procedures for all subjects. Any subject receiving anticoagulant therapy should have coagulation factors monitored closely throughout the trial.
[e] Free T3 is preferred; if not available total T3 may be tested.

Laboratory tests for screening should be performed within 10 days prior to the first dose of trial treatment. After Cycle 1, pre-dose laboratory procedures can be conducted up to 72 hours prior to dosing. Results must be reviewed by the investigator or qualified designee and found to be acceptable prior to each dose of trial treatment.

7.1.3.2 Pharmacokinetic Evaluations

To further evaluate pembrolizumab immunogenicity and exposure in these indications, and also to evaluate exposure during 200 mg fixed Q3W dosing, sample collections for analysis of PK are currently planned as shown in the Trial Flowchart (Sections 6.1). However, if ongoing pembrolizumab trial PK results continue to be consistent with existing PK data (derived mainly in subjects with melanoma and NSCLC), the Sponsor may elect to discontinue further sample collection for this purpose in this trial.

7.1.3.2.1 Blood Collection for Serum Levels of MK-3475

Sample collection, storage and shipment instructions for serum PK samples will be provided in the Procedures Manual. PK samples should be drawn for all subjects.

7.1.3.3 Blood Collection for Planned Genetic Analysis

At the time of blood collection prior to the initial dose of pembrolizumab, whole blood will be collected for Planned Genetic Analysis.

7.1.3.4 Blood Collection for Correlative Studies and Biomarker Assessment

Sample collection, processing, storage, and shipment instructions for blood samples collected for correlative studies and for evaluation of multiple different biomarkers are provided in the Procedures Manual. Any leftover samples from the correlative and biomarker samples will be stored for future biomedical research if the subject signs the FBR consent.

7.1.4 Tumor Imaging and Assessment of Disease

The process for image collection and transmission to the independent central imaging vendor can be found in the Site Imaging Manual. Tumor imaging should be performed by computed tomography (CT) (preferred), unless indicated otherwise in the Site Imaging Manual. Magnetic resonance imaging (MRI) should be used only when CT is contraindicated, for imaging of the CNS, or for certain anatomical regions in specific cohorts (See Site Imaging Manual). The same imaging technique with respect to the modality and use of contrast should be used in a subject throughout the trial to optimize the visualization of existing and new tumor burden.

Determination of measurable disease based on RECIST 1.1 will be conducted by the local site investigator during screening for initial assessment of subject eligibility. Confirmation of measurable disease by the central imaging vendor per RECIST 1.1 is required prior to subject enrollment. All scheduled images for all subjects will be submitted to the central imaging vendor. In addition, if the site obtains additional imaging, including other modalities, that are obtained at an unscheduled time point to determine if the subject has progressed as well as imaging obtained for other reasons but captures radiologic progression, all of these imaging scans should be sent to the central imaging vendor.

7.1.4.1 Initial Tumor Imaging

Initial tumor imaging must be performed within 28 days prior to the first dose of trial treatment. Each subject's baseline imaging scan must be submitted to the central imaging

vendor for confirmation of measurable disease per RECIST 1.1. Only subjects with confirmation of measurable disease by RECIST 1.1 as assessed by such independent central radiologic review will be eligible to participate in the trial. If this independent central radiologic review of the initial tumor imaging study fails to confirm measureable disease per RECIST 1.1, the subject will be considered a screen failure and will not be treated.

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 for a given subject throughout the trial.

7.1.4.2 Tumor Imaging During Trial

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

The first imaging assessment during treatment should be performed at 9 weeks (63 ±7 days) from Cycle 1, Day 1. Subsequent imaging should initially be performed every 9 weeks (63 ±7 days) or more frequently if clinically indicated. After the first 12 months on trial therapy, the imaging interval should be increased to every 12 weeks (84 ±7 days). Imaging timing should follow calendar days and should not be adjusted for delays in cycle starts. Imaging should continue to be performed until disease progression (unless the investigator elects to continue treatment and follow irRECIST) (see Section 5.8.1), the start of new anti-cancer treatment, withdrawal of consent, death, or notification by the Sponsor, whichever occurs first. All supplemental imaging which documents PD must be submitted to the central imaging vendor.

Per RECIST 1.1, PRs and CRs should be confirmed by a repeat tumor imaging assessment not less than 4 weeks from the date the response was first documented. The tumor imaging for confirmation of response may be performed at the earliest 4 weeks after the first indication of response, or at the next scheduled scan (i.e., 9 weeks later). Subjects will then return to regular scheduled imaging every 9 weeks, starting with the next scheduled imaging time point. Subjects who obtain a confirmation scan do not need to undergo the next scheduled tumor imaging if it is < 4 weeks later; tumor imaging may resume at the subsequent scheduled imaging time point.

If irRECIST is used for clinical management (see Section 5.8.1), disease progression should be confirmed by the investigator at least 4 weeks after the 1st investigator-assessed PD or at the next scheduled time point after radiologic evidence of PD in clinically stable subjects. Per irRECIST, subjects who have unconfirmed disease progression may continue on treatment at the discretion of the investigator until progression is confirmed by the site provided they have met the conditions detailed in Section 5.8.1. Subjects who obtain a confirmation scan do not need to undergo the next scheduled tumor imaging if it is < 4 weeks later; tumor imaging may resume at the subsequent scheduled imaging time point if clinically

stable. Subjects who have confirmed PD as assessed by the investigator will discontinue treatment. Exception is detailed in Section 7.1.4.7.1.

In subjects who discontinue trial therapy without local investigator verified PD, tumor imaging should be performed at the time of treatment discontinuation (i.e., date of discontinuation ± 4 week window). If previous tumor imaging was obtained within 4 weeks prior to the date of discontinuation, then tumor imaging at treatment discontinuation is not necessary.

Imaging should continue to be performed until PD is documented by local investigator assessment (or in cases were the investigator elects to continue treatment and follow irRECIST (see Section 5.8.1), confirmed by local investigator assessment of a repeat imaging study ≥ 4 weeks later), the start of new anti-cancer treatment, withdrawal of consent, death, or the end of the trial, whichever occurs first.

7.1.4.3 Brain Imaging

Subjects with previously treated brain metastases may participate provided these brain metastases are stable, with no evidence of progression by imaging over a period of at least 4 weeks and confirmed by imaging (using MRI, if MRI was used at prior imaging, or CT imaging, if CT was used at prior imaging) within 28 days of the first dose of trial treatment. The stability of such brain metastases will be assessed and confirmed locally and will not require central confirmation. Also, any neurologic symptoms must have returned to baseline, and the subject must not have received corticosteroids for the treatment of brain metastases for at least 7 days prior to trial initiation as per local site assessment. This exception does not include carcinomatous meningitis, as subjects with carcinomatous meningitis are excluded regardless of clinical stability. For subjects with stable brain metastases enrolled in the trial, the baseline brain image must be submitted to the central imaging vendor to be held for possible future analysis. For any subject with known stable brain metastases at baseline and who achieves a CR during trial treatment, follow-up brain imaging is required for confirmatory assessment of CR. This image will be submitted for independent central radiologic review.

Subjects with small cell lung or thyroid cancer (without a history of stable brain metastases) may participate provided they undergo a brain scan within 28 days prior to the first dose of trial treatment, with local confirmation that no brain metastases are present. For those subjects with these two tumor types subsequently enrolled in the trial, this baseline brain scan should be submitted to the central imaging vendor, but independent central radiologic confirmation of a lack of brain metastases is not required.

7.1.4.4 Imaging for Bone Metastases

For any subject with an elevated baseline serum alkaline phosphatase level (>1.5x upper limit of normal range), bone imaging (e.g. bone scan or PET scan) must be performed to identify possible bone metastases. If bone metastases are identified that have not been imaged on the CT/MRI performed for Initial Tumor Imaging (Section 7.1.4.1 above), then additional baseline and all subsequent tumor imaging studies must include such lesions in the imaging field.

7.1.4.5 Second Course Phase (Retreatment) Tumor Imaging

Tumor imaging must be performed within 28 days prior to restarting treatment with pembrolizumab.

The first on-study imaging assessment should be performed at 9 weeks (63 days ±7 days) after the restart of treatment. Subsequent tumor imaging should be performed every 9 weeks (63 days ±7 days) or more frequently if clinically indicated. After the first 12 months on the second course of therapy, the imaging interval should be increased to every 12 weeks (84 days ±7 days). Imaging should not be delayed for delays in cycle starts of pembrolizumab treatment.

When irRECIST is used for clinical management (see Section 5.8.1), if tumor imaging demonstrates 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 is confirmed by the local site investigator, the start of new anti-cancer 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.

7.1.4.6 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 PD verified by the local investigator, this is the final required tumor imaging.

In subjects who discontinue trial treatment without local investigator-documented disease progression, every effort should be made to continue monitoring their disease status by radiologic imaging every 12 weeks (84 ± 7 days) in the first year, and every 24 weeks (168 ± 7 days) after year 1 until (1) the start of new anti-cancer treatment, (2) disease progression verified by the local investigator, (3) death, or (4) the end of the trial, whichever occurs first.

All tumor imaging (scheduled and unscheduled) should be submitted to the central imaging vendor for analysis. In addition, if the investigator obtains additional imaging, including other modalities, that are obtained at an unscheduled time point to determine if the subject has progressed as well as imaging obtained for other reasons but captures radiologic progression, all of these imaging scans should be sent to the central imaging vendor.

7.1.4.7 Assessment of Disease

For the purposes of assessing primary and secondary trial endpoints, RECIST 1.1 (Appendix 12.7) will be applied by the central imaging vendor as the primary measure for assessment of

tumor burden and date of disease progression. To address exploratory endpoints, irRECIST will also be applied by the central imaging vendor for each imaging study evaluated by RECIST 1.1.

If RECIST 1.1-determined PD is restricted to a solitary lesion, its neoplastic nature must be confirmed either by cytology/histology or by lesion progression on the next imaging examination.

All clinically stable subjects who have unconfirmed recurrent disease will be managed as detailed in Section 5.8.1. All scans, including confirmatory scans, should be submitted to the central imaging vendor for evaluation.

Independent central radiologic review will be used to confirm the subject eligibility requirement for measureable disease (See Site Imaging Manual for detailed steps). Confirmatory scans performed as detailed in Section 5.8.1 will be evaluated locally by the investigator for the purpose of clinical decision-making. The central imaging vendor will receive all images from the sites and will analyze treatment responses by RECIST 1.1 and irRECIST.

In subjects who discontinue study therapy without documented disease progression, every effort should be made to continue monitoring their disease status by tumor imaging every 12 weeks (84 ± 7 days) in the first year, and every 24 weeks (168 ± 7 days) after year 1 until (1) the start of new anti-cancer treatment, (2) disease progression (3) death, or (4) the end of the study, whichever occurs first.

7.1.4.7.1 Exception to Discontinuation of Pembrolizumab Treatment Following Confirmed Progression of Disease

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

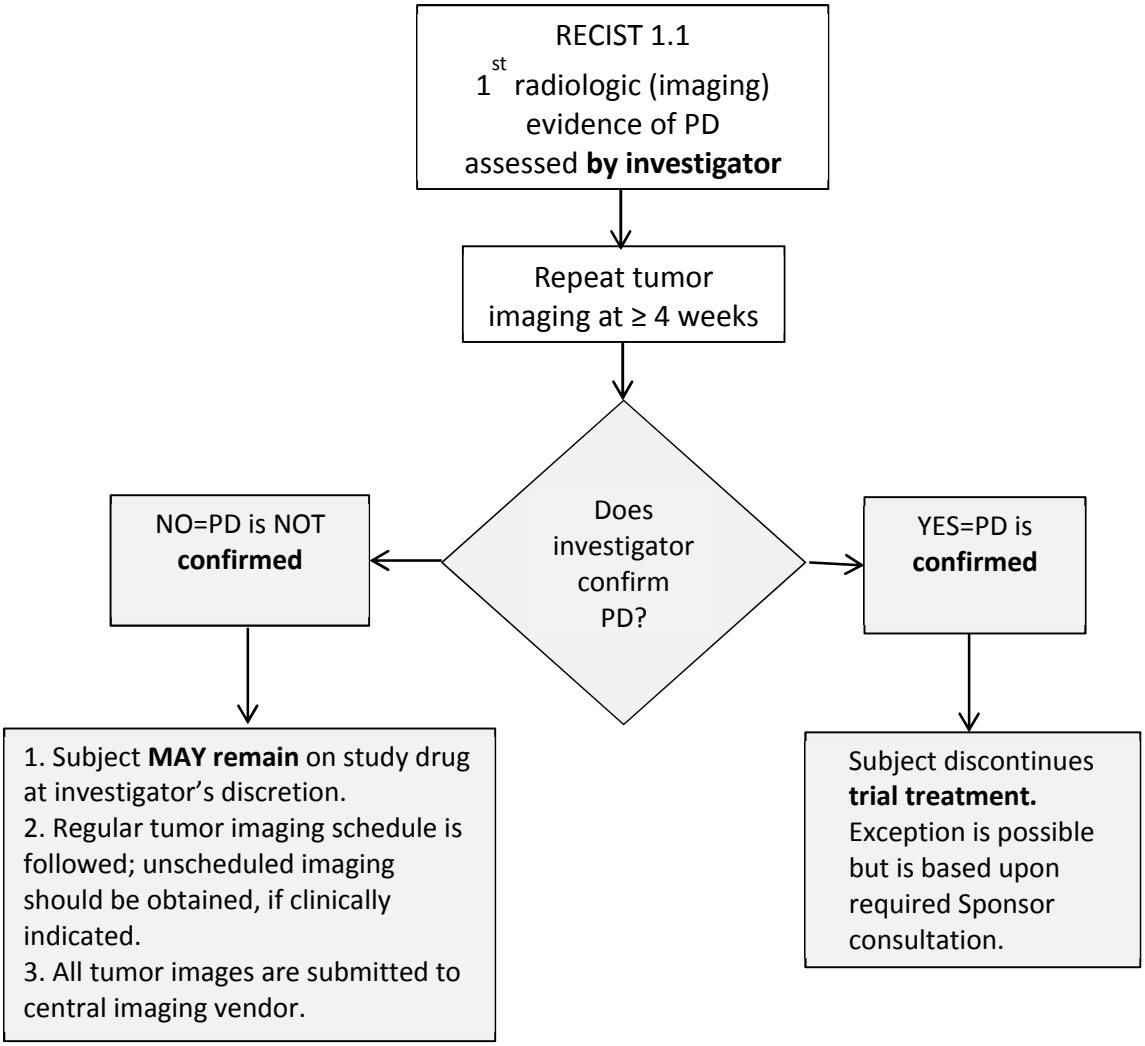

Figure 2 Imaging and Treatment for Clinically Stable Subjects After First Radiologic Evidence of PD Assessed by the Site (irRECIST-based Management)

7.1.5 Tumor Tissue Collection

A tumor tissue sample must be submitted to the central laboratory for characterization of PD-L1 expression, GEP, and MSI for all subjects being considered for enrollment in Groups A-J. A new tumor specimen (defined as a tumor specimen collected since the completion of the most recent cancer therapy), if obtained as part of normal clinical practice (not solely for the purpose of screening for enrollment in this study) is preferred to archival samples. If collection of such a new tumor specimen for this study would require a procedure, not otherwise clinically indicated, that would create significant risk for the subject (including (but not limited to) biopsies of the brain, lung/mediastinum, pancreas, or endoscopic procedures extending beyond the esophagus, stomach or bowel), an archival specimen should be submitted. The submitted tumor tissue specimen must be of sufficient quality and quantity for assessment of all three of these primary biomarkers. All secondary and

exploratory tumor biomarkers will also be assessed using tissue from the same tumor specimen.

Submission of an FFPE tumor tissue block is preferred, while submission of slides cut from a tissue block or tumor tissue from a new biopsy in formalin is also acceptable. Tumor tissue fixed in any fixative other than formalin is not acceptable. If unstained slides are submitted, the slides must be freshly cut and submitted to the testing laboratory within 10 days from the slide sectioning date. All submitted slides must be cut from a single tumor tissue sample specimen. The site must ensure that the newly obtained tissue sample collection date and slide cut date are documented in the source and/or tissue submission forms. Slides submitted more than 10 days after cutting or cut from more than one tissue specimen block will be rejected and a new specimen will be required.

In cases in which an adequate amount of tumor tissue has not been provided to allow for evaluation of all three primary biomarkers for subjects in Groups A-J, additional tumor tissue must be provided. If additional tumor tissue from the same specimen is available, tumor tissue from that specimen of sufficient quantity and quality for assessment of the remaining required biomarkers must be submitted. If a sufficient amount of additional tumor tissue from the same specimen is NOT available, tissue from a different tumor specimen of sufficient quantity and quality for assessment of all three primary biomarkers must be submitted. If a subject being considered for enrollment into Groups A-J has a tumor that tests positive for MSI-H but has insufficient tumor for evaluation of all three primary biomarkers, that subject may be enrolled in cohort K after consultation with and approval by the Sponsor. Analysis of all secondary and exploratory biomarkers should be performed using slides/tissue from the same tumor tissue specimen as was used for assessment of the three primary biomarkers.

After interim analyses, subsequent enrollment of subjects into Groups A-J may be based on tumor expression of one or more primary biomarker(s) (biomarker enrichment). In such cases, tumor tissue must be positive for the selected entry primary biomarker(s) prior to subject enrollment.

For enrollment in Group K, a tumor tissue sample must test positive for MSI-H. A newly obtained tumor specimen is also preferred to an older archival sample for MSI testing. For the initial approximately 100 subjects in this Group, submission of tumor tissue from the same specimen used for MSI testing for evaluation of the other two primary biomarkers (PD-L1 and GEP) will be requested (but is not required). For subsequent subjects enrolled in this Group, submission of tissue for subsequent retrospective MSI testing is required, while tissue for the evaluation of the other two primary biomarkers (PD-L1 and GEP) will be requested (but is not required).

For all subjects, submission of a sample of whole blood collected into an EDTA tube for DNA extraction for MSI testing is also required. This collection and submission must occur sometime during the Screening period.

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

7.1.6 Patient Reported Outcomes (PROs)

The EuroQol EQ-5D and EORTC QLQ-C30 questionnaires will be administered by trained site personnel and completed electronically by subjects in the following order: EuroQol EQ-5D first then EORTC QLQ-C30 at the time points specified in the Trial Flow Chart. All electronic PROs (ePROs) should be administered prior to drug administration, AE evaluation and tumor imaging.

7.1.7 Future Biomedical Research

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

- Remaining DNA for future use
- Remaining tumor tissue
- Remaining DNA and RNA from correlative samples
- Remaining plasma and serum from biomarker samples

7.1.8 Other Procedures

7.1.8.1 Withdrawal/Discontinuation

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

When a subject discontinues/withdraws from participation in the trial, all applicable activities scheduled for the final 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.

7.1.8.1.1 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.

7.1.8.1.2 Lost to Follow-up

If a subject fails to return to the clinic for a required study visit and/or if the site is unable to contact the subject, the following procedures are to be performed:

- The site must attempt to contact the subject and reschedule the missed visit. If the subject is contacted, the subject should be counseled on the importance of maintaining the protocol-specified visit schedule.
- The investigator or designee must make every effort to regain contact with the subject at each missed visit (e.g. phone calls and/or a certified letter to the subject's last known mailing address or locally equivalent methods). These contact attempts should be documented in the subject's medical record.

Note: A subject is not considered lost to follow up until the last scheduled visit for the individual subject. The amount of missing data for the subject will be managed via the pre-specified data handling and analysis guidelines.

7.1.8.2 Blinding/Unblinding

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

7.1.8.3 Calibration of Critical Equipment

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

Critical Equipment for this trial includes:

- Laboratory equipment – as required for inclusion laboratory tests and trial assessments
- Imaging equipment – as required for trial objectives

See protocol-specified guidance in the Administrative Binder, Procedures Manual, Pharmacy Manual and Site Imaging Manual.

7.1.9 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.

7.1.9.1 Screening

Within 42 days prior to enrollment, potential subjects will be evaluated to determine if they fulfill the entry requirements as set forth in Section 5.1. Screening procedures may be repeated after consultation with and approval by the Sponsor.

Subjects who have a tumor tissue sample available for biomarker analysis, or who need a new tumor biopsy procedure performed specifically to obtain tumor tissue for biomarker analysis will sign the informed consent form. After providing consent, subjects 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 42 days prior to the first dose of trial treatment except for the following:

- The informed consent form must be signed prior to completing any protocol-specified procedure.
- ECOG for screening is to be performed within 3 days of the first dose. The laboratory tests for screening are to be performed within 10 days prior to the first dose of pembrolizumab.
- 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).
- Imaging for baseline tumor assessment (all subjects) and for brain evaluation (selected subjects as described in Section 7.1.4.3) is to be performed within 28 days prior to the first dose of trial medication.

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.

7.1.9.2 Treatment Period

Visit requirements are outlined in Section 6.0 – Trial Flow Chart. Specific procedure-related details are provided above in Section 7.0 – Trial Procedures.

7.1.9.2.1 Second Course Phase (Retreatment Period)

Subjects who stop pembrolizumab (MK-3475) with SD or better may be eligible for up to one year of additional pembrolizumab (MK-3475) 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 (MK-3475) 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, or
        - Was treated with at least 8 administrations of pembrolizumab and received at least two treatments with pembrolizumab beyond the date when the initial CR was declared

      OR
    - Subject had SD, PR or CR and stopped pembrolizumab (MK-3475) treatment after completing a full course of 24 months of study therapy. **AND**
- Experienced an investigator-determined confirmed radiographic disease progression after stopping their initial treatment with pembrolizumab
- Did not receive any anti-cancer treatment since the last dose of pembrolizumab
- Have a performance status of 0 or 1 on the ECOG Performance Scale within 3 days of the first retreatment dose of pembrolizumab
- Demonstrate adequate organ function as detailed in Section 5.1.2
- Female subject of childbearing potential should have a negative urine or serum pregnancy test within 72 hours prior to receiving retreatment with study medication.
- Female subjects of childbearing potential (See Section 5.7.2) must be willing to use an adequate method of contraception, as outlined in Section 5.7.2. – Contraception, for the course of the study through 120 days after the last dose of trial medication.

  Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception method for the subject.
- Male subjects of childbearing potential (See Section 5.7.2.) must agree to use an adequate method of contraception, as outlined in Section 5.7.2. – Contraception, for the course of the study through 120 days after the last dose of trial medication.

  Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception method for the subject
- Does not have a history or current evidence of any condition, therapy, or laboratory abnormality that might interfere with the subject's participation for the full duration of the trial or is not in the best interest of the subject to participate, in the opinion of the treating investigator.

Subjects who restart treatment will be retreated at the same dose frequency as when they last received pembrolizumab (MK-3475). Treatment will be administered for up to 17 additional doses (approximately one additional year of treatment).

Visit requirements are outlined in Section 6.2 – Trial Flow Chart – Second Course Phase (Retreatment).

7.1.9.3 Post-Trial

7.1.9.3.1 Safety Follow-Up Visit

The mandatory Safety Follow-Up Visit should be conducted approximately 30 (±7) days after the last dose of trial treatment or before the initiation of a new anti-cancer treatment, whichever comes first. All AEs that occur prior to the Safety Follow-Up Visit should be recorded. Subjects with an AE of Grade > 1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new anti-cancer therapy, whichever occurs first. SAEs that occur within 90 days of the end of treatment or before initiation of a new anti-cancer treatment should also be followed and recorded.

Subjects who are eligible for retreatment with pembrolizumab (as described in Section 2.1 and 7.1.9.2.1) may have up to two safety follow-up visits, one after the Treatment Period and one after the Second Course Phase.

7.1.9.3.2 Follow-up Visits

Subjects who discontinue trial treatment for a reason other than disease progression will move into the Follow-Up Phase and should be assessed as described in Section 6.1 to monitor disease status. Every effort should be made to collect information regarding disease status until the start of new anti-cancer therapy, locally assessed disease progression, death, end of trial or if the subject begins retreatment with pembrolizumab as detailed in Section 2.1.

Information regarding post-study anti-cancer treatment will be collected if a new treatment is initiated.

Eligible subjects with local investigator-assessed PD who enter the retreatment phase of the trial according to the criteria in Section 2.1 and Section 7.1.9.2.1 will move from post-treatment follow-up in the Initial Treatment Phase (Section 6.1) to the Second Course Phase. Details are provided in Section 6.2 (Second Course Phase (Retreatment) Flowchart).

7.1.9.3.3 Survival Follow-up

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

7.1.9.4 Survival Status

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

7.2 Assessing and Recording Adverse Events

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

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

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

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

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

All adverse events that occur after the consent form is signed but before randomization/treatment allocation must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure. From the time of randomization/ treatment allocation through 30 days following cessation of treatment, all adverse events must be reported by the investigator. Such events will be recorded at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in section 7.2.3.1. The investigator will make every attempt to follow all subjects with non-serious adverse events for outcome.

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

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

For purposes of this trial, an overdose of pembrolizumab will be defined as any dose of 1,000 mg or greater (≥5x the indicated dose). No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

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

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

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

7.2.2 Reporting of Pregnancy and Lactation to the Sponsor

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

Pregnancies and lactations that occur after the consent form is signed but before randomization/treatment allocation must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure. Pregnancies and lactations that occur from the time of randomization/treatment allocation through 120 days following cessation of Sponsor's product or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, must be reported by the investigator. All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

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

7.2.3 Immediate Reporting of Adverse Events to the Sponsor

7.2.3.1 Serious Adverse Events

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

- Results in death;
- Is life threatening;
- Results in persistent or significant disability/incapacity;
- Results in or prolongs an existing inpatient hospitalization;

- Is a congenital anomaly/birth defect;
- Is an other important medical event.

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

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

Refer to Table 12 for additional details regarding each of the above criteria.

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

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

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

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

7.2.3.2 Events of Clinical Interest

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

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

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

Events of clinical interest for this trial include:

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

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

7.2.3.3 Protocol-Specific Exceptions to Serious Adverse Event Reporting

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

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

The Sponsor will monitor 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 12 Evaluating Adverse Events

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

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

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

7.2.5 Sponsor Responsibility for Reporting Adverse Events

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

8.0 STATISTICAL ANALYSIS PLAN

The study uses an adaptive approach. Safety and efficacy data will be reviewed in an ongoing basis. The accrual of this study will also be evaluated and updated as the trial evolves. This section outlines the broad statistical analysis plan for this trial. The detailed statistical analysis strategy and procedures will be documented separately in a supplemental statistical analyses plan (sSAP), which will be updated periodically as the trial evolves.

8.1 Statistical Analysis Plan Summary

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

Study Design Overview	A Clinical Trial of Pembrolizumab (MK-3475) Evaluating Predictive Biomarkers in Subjects with Advanced Solid Tumors (KEYNOTE 158)
Treatment Assignment	Pembrolizumab 200 mg IV Q3W, single treatment arm, open-label.
Analysis Populations	Efficacy and Safety: All Subjects as Treated (ASaT)
Primary Endpoint(s)	ORR based on RECIST 1.1 as assessed by independent central radiologic review
Key Secondary Endpoints	DOR PFS OS
Statistical Methods for Key Efficacy/Immunogenicity/ Pharmacokinetic Analyses	For ORR, the point estimate and exact Clopper-Pearson confidence interval (CI) will be provided.
Statistical Methods for Key Safety Analyses	Safety will be evaluated using descriptive statistics.
Interim Analyses	Multiple interim analyses will be performed.
Multiplicity	There is no planned multiplicity control for this trial.
Sample Size and Power	A minimum of 200 subjects and a maximum of up to approximately 1350 subjects will be enrolled in this trial over a period of approximately 90 months. It is the intent to initially enroll approximately 50 biomarker unselected subjects with each of ten tumor types (Groups A- J) (approximately 500 subjects). The study may enroll approximately 50 additional subjects in each tumor type in Group (A-J) either regardless of primary biomarker status or based on tumor expression of selected primary biomarker(s) (biomarker enrichment) (approximately 500 additional subjects). In addition, the study may enroll up to approximately 350 subjects in Group K (MSI-H).

8.2 Responsibility for Analyses/In-House Blinding

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

The Sponsor will generate the allocation schedule(s) for study treatment assignment and subject allocation will be implemented in IVRS.

Although the trial is open label, independent radiologist(s) will perform the central imaging review without knowledge of subject-level biomarker status.

8.3 Hypotheses/Estimation

Objectives of the trial are stated in Section 3.0.

8.4 Analysis Endpoints

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

8.4.1 Efficacy Endpoints

The primary efficacy endpoint is **ORR,** defined as the proportion of subjects who have a CR or PR using RECIST 1.1 at any time during the trial. Response for the primary analysis will be determined by independent central radiologic review, with confirmatory assessment as required per RECIST 1.1. Subjects with unknown or missing response information will be treated as non-responders.

Secondary efficacy endpoints include:

(1) **DOR,** defined in the subset of subjects with a CR or PR, based on RECIST 1.1 as assessed by independent central radiologic review, as the time from first documented evidence of CR or PR until the first documented sign of disease progression or death due to any cause, whichever occurs first. Subjects who are alive, have not progressed, have not initiated new anti-cancer treatment, and have not been determined to be lost to follow-up are considered ongoing responders at the time of analysis.

(2) **PFS,** defined as the time from allocation to the first documented disease progression according to RECIST 1.1, as assessed by independent central radiologic review, or death due to any cause, whichever occurs first. If a subject does not have a documented date of progression or death, PFS will be censored at the date of the last adequate assessment.

(3) **OS,** defined as the time from the date of allocation to the date of death due to any cause. Censoring will be performed using the date of last known contact for those who are alive at the time of analysis.

8.4.2 Safety Endpoints

A description of safety endpoint assessment 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. Other safety endpoints include laboratory safety assessments, ECOG performance status, vital signs and physical examinations.

8.4.3 Exploratory Endpoints

PFS, ORR and DOR per irRECIST are defined as specified for the respective endpoints using RECIST 1.1 above, with the exception that a confirmatory assessment of PD (at least 4 weeks after the initial PD assessment) is required for subjects who remain on treatment following initial evidence of PD per RECIST 1.1. Subjects being managed by irRECIST who discontinue treatment following confirmation of PD per irRECIST will be counted as having disease progression on the date of the initial PD assessment.

8.5 Analysis Populations

Subjects are enrolled in the trial when they have received an allocation number via IVRS (see Section 5.3).

8.5.1 Efficacy Analysis Populations

The ASaT population will be used for the analysis of efficacy in this trial. The ASaT population consists of all allocated subjects who have received at least one dose of study treatment.

8.5.2 Safety Analysis Populations

The ASaT population will be used for the analysis of safety data in this trial. At least one laboratory or vital sign measurement obtained subsequent to at least one dose of study treatment is required for inclusion in the analysis of each specific parameter. To assess change from baseline, a baseline measurement is also required.

8.6 Statistical Methods

8.6.1 Statistical Methods for Efficacy Analyses

The primary efficacy endpoint is ORR based on RECIST 1.1, as assessed by independent central radiologic review. The point estimate and exact Clopper-Pearson CI will be provided. Secondary efficacy endpoints of DOR, PFS, and OS will be summarized.

Censoring rules for DOR are summarized in Table 13. Subjects who have not progressed, have not initiated a new anti-cancer treatment, and have not died at the time of analysis are considered as ongoing responders at the time of analysis.

Table 13 Censoring Rules for Duration of Response

Situation	**Date of Progression or Censoring**	**Outcome**
No progression nor death, no new anti-cancer therapy initiated	Last adequate disease assessment	Censor (non-event)
No progression nor death, new anti-cancer therapy initiated	Last adequate disease assessment before new anti-cancer therapy initiated	Censor (non-event)
Death or progression after ≥ 2 missed adequate disease assessments	Last adequate disease assessment prior to the after ≥ 2 missed adequate disease assessments	Censor (non-event)
Death or progression after ≤ 1 missed adequate disease assessments	PD or death	End of response (Event)
Patients are considered to have an ongoing response if censored, alive, have not progressed, and have not started a new anti-cancer therapy and have not been lost to follow-up (i.e., Situation 1 in the first row of the table)		

For DOR, if data warrant, Kaplan-Meier medians and quartiles will be provided. Descriptive summaries including swim lane plots will also be provided. For PFS and OS, if data warrant, Kaplan-Meier quartile estimates along with the 95% CI will be provided.

Further details will be provided in the sSAP. Table 14 summaries the analysis strategy for the key efficacy variables as below.

Table 14 Analysis Strategy for Key Efficacy Variables

Endpoint/Variable (Description, Time Point)	Statistical Method	Analysis Population	Missing Data Approach
Primary Objectives			
ORR per RECIST 1.1 by central radiologic assessment	Exact test of binomial parameter, 95% CI calculated using the Clopper-Pearson method	ASaT	Subjects with missing data are considered non-responders
Secondary Objectives			
DOR per RECIST 1.1 by central radiologic assessment	Summary statistics using Kaplan-Meier method	All responders	Non-responders are excluded in analysis
PFS per RECIST 1.1 by central radiologic assessment	Summary statistics using Kaplan-Meier method	ASaT	Censored at last assessment
OS	Summary statistics using Kaplan-Meier method	ASaT	Censored at last assessment

Further details on the statistical approach of efficacy analysis will be described in the sSAP.

8.6.2 Statistical Methods for Safety Analyses

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

Adverse Events

AEs will be coded using the standard MedDRA and grouped system organ class. AEs will be graded by the investigator according to CTCAE, version 4.0.

Events will be summarized based on frequency and proportion of total subjects, by system organ class and preferred term. Separate summaries with descriptive statistics (counts, percentage, mean, standard deviation, etc.) will be given for all AEs, treatment-related AEs, AEs by toxicity grade, SAEs and AEs leading to discontinuation of study treatment and dose modification.

ECIs will be identified and additional summaries provided.

The incidence of deaths and the primary cause of death will be summarized.

Further details on the statistical approach of safety analysis will be described in the sSAP.

8.6.3 Summaries of Baseline Characteristics, Demographics, and Other Analyses

Baseline characteristics will be assessed by the use of tables and/or graphs. No statistical hypothesis tests will be performed on these characteristics. The number and percentage of subjects screened, 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.

8.6.3.1 Patient-Reported Outcomes Analyses

EORTC QLQ-C30 and EuroQoL EQ-5D data will be summarized as part of the pre-specified exploratory analysis. Patient-reported treatment effects will be evaluated at pre-specified time points while on treatment and 30 days following treatment discontinuation as measured by change from baseline in the QLQ-C30 QoL domain and all sub-scales/single items. In addition to the estimated mean effects, cumulative distribution and the number and proportion of patients who “improved”, “worsened”, or “remained stable” from baseline to a pre-defined visit will also be estimated. For EQ-5D, pre-specified exploratory analyses will be performed to describe the distribution of responses. Additional details will be included in the sSAP.

8.7 Interim Analyses

The trial incorporates an adaptive design in which multiple interim analyses may be performed. Results will be reviewed by the study team. The cutoffs for the three primary biomarker assays will be selected and specified before the first interim analysis. Details regarding the timing and conduct of the initial interim analysis will be further clarified in the sSAP. The planned sample size may be modified based on the interim results. The timing of

additional interim analyses, the final analysis as well as the analysis plan will be documented in the sSAP. The sSAP will also be updated as the trial evolves.

The primary endpoint of ORR will be used for all interim analyses. At each interim analysis, ORR in both biomarker selected and unselected populations will be summarized along with corresponding DOR.

The primary endpoint of ORR will be used for all interim analyses with or without a confirmatory assessment; however, a confirmatory assessment is required for the final analysis.

8.8 Multiplicity

The study is an adaptive trial. The cumulative data will be reviewed by the study team on an ongoing basis, with no multiplicity control.

8.9 Sample Size and Power Calculations

A minimum of 200 subjects and a maximum of up to approximately 1350 subjects will be enrolled in this trial over a period of approximately 90 months. It is the intent to enroll approximately 50 subjects regardless of biomarker status in each of the ten specified tumor types (Group A- J).

If all tumor types enroll the maximum of 50 subjects, this will result in no more than 500 subjects in this initial phase of the trial. The study also allows enrollment of approximately 50 additional subjects in each of the ten specified tumor types either tumor biomarker unselected or based on tumor biomarker expression (biomarker enrichment). This may result in enrollment of approximately 500 additional subjects. In addition, the study may enroll up to approximately 350 subjects in the MSI-H Group K.

In this study, the sample size and the underlying response rate are unknown. Therefore, no power calculations have been incorporated into this study.

8.10 Subgroup Analyses and Effect of Baseline Factors

Efficacy will be evaluated separately in each biomarker selected subgroup, including calculation of efficacy across pooled histologies, as well as individually for each histology. For the PD-L1 and GEP primary biomarkers, response data from subjects in Groups A-J will be utilized for this purpose, while for MSI-H, response data from subjects in Groups A-K will be utilized. For the best overall response rate based on RECIST 1.1, the point estimate and 95% CI will be provided using the Clopper-Pearson exact method based on binomial distribution. Subjects without response data will be counted as non-responders. A confirmatory assessment will be required for all subjects who experience a CR or PR.

8.11 Compliance (Medication Adherence)

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

8.12 Extent of Exposure

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 the 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 15.

Clinical supplies will be packaged to support enrollment and replacement subjects as required. When a replacement subject is required, the Sponsor or designee needs to be contacted prior to dosing the replacement supplies.

Table 15 Product Descriptions

Product Name & Potency	Dosage Form
Pembrolizumab 25 mg/mL	Solution for Infusion

All other supplies not indicated in Table 15 above will be provided centrally by the Sponsor or locally by the trial site, subsidiary or designee, depending on local country operational or regulatory requirements.

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

9.2 Packaging and Labeling Information

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

Subjects will receive open label supply as non-kitted single vials. All supplies will be provided as open label. Pembrolizumab will be provided as non-kitted single vials or as single vials in a kit box.

9.3 Clinical Supplies Disclosure

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

9.4 Storage and Handling Requirements

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

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

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

9.5 Discard/Destruction/Returns and Reconciliation

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

9.6 Standard Policies

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

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

10.1 Confidentiality

10.1.1 Confidentiality of Data

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

10.1.2 Confidentiality of Subject Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), IRB/ERC, or regulatory authority representatives may consult and/or copy trial documents in order to verify worksheet/case report form data. By signing the consent form, the subject agrees to this process. If trial documents will be photocopied during the process of verifying

worksheet/case report form information, the subject will be identified by unique code only; full names/initials will be masked prior to transmission to the Sponsor.

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

10.1.3 Confidentiality of Investigator Information

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

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

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

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

10.1.4 Confidentiality of IRB/IEC Information

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

10.2 Compliance with Financial Disclosure Requirements

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

The investigator/subinvestigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor to

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

10.3 Compliance with Law, Audit and Debarment

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

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

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

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

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

Trial documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the trial site upon request for inspection, copying, review and audit at reasonable times by representatives of the Sponsor or any regulatory authorities. The investigator agrees to promptly take any reasonable steps that are requested by the Sponsor as a result of an audit to cure deficiencies in the trial documentation and worksheets/case report forms.

The investigator must maintain copies of all documentation and records relating to the conduct of the trial in compliance with all applicable legal and regulatory requirements. This documentation includes, but is not limited to, the protocol, worksheets/case report forms, advertising for subject participation, adverse event reports, subject source data, correspondence with regulatory authorities and IRBs/ERCs, consent forms, investigator's curricula vitae, monitor visit logs, laboratory reference ranges, laboratory certification or

quality control procedures and laboratory director curriculum vitae. By signing this protocol, the investigator agrees that documentation shall be retained until at least 2 years after the last approval of a marketing application in an ICH region or until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. Because the clinical development and marketing application process is variable, it is anticipated that the retention period can be up to 15 years or longer after protocol database lock. The Sponsor will determine the minimum retention period and notify the investigator when documents may be destroyed. The Sponsor will determine the minimum retention period and upon request, will provide guidance to the investigator when documents no longer need to be retained. The sponsor also recognizes that documents may need to be retained for a longer period if required by local regulatory requirements. All trial documents shall be made available if required by relevant regulatory authorities. The investigator must consult with and obtain written approval by the Sponsor prior to destroying trial and/or subject files.

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

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

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

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

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

10.4 Compliance with Trial Registration and Results Posting Requirements

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

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

10.5 Quality Management System

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

10.6 Data Management

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

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

10.7 Publications

This trial is intended for publication, even if terminated prematurely. Publication may include any or all of the following: posting of a synopsis online, abstract and/or presentation at a scientific conference, or publication of a full manuscript. The Sponsor will work with the authors to submit a manuscript describing trial results within 12 months after the last data become available, which may take up to several months after the last subject visit in some cases such as vaccine trials. However, manuscript submission timelines may be extended on OTC trials. For trials intended for pediatric-related regulatory filings, the investigator agrees to delay publication of the trial results until the Sponsor notifies the investigator that all relevant regulatory authority decisions on the trial drug have been made with regard to

pediatric-related regulatory filings. Merck will post a synopsis of trial results for approved products on www.clinicaltrials.gov by 12 months after the last subject's last visit for the primary outcome, 12 months after the decision to discontinue development, or product marketing (dispensed, administered, delivered or promoted), whichever is later.

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

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

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

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

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12.0 APPENDICES

12.1 Merck Code of Conduct for Clinical Trials

Merck*

Code of Conduct for Clinical Trials

I. Introduction

A. Purpose

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

B. Scope

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

II. Scientific Issues

A. Trial Conduct

1. Trial Design

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

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

2. Site Selection

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

3. Site Monitoring/Scientific Integrity

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

B. Publication and Authorship

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

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

III. Subject Protection

A. IRB/ERC review

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

B. Safety

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

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

C. Confidentiality

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

D. Genomic Research

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

IV. Financial Considerations

A. Payments to Investigators

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

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

B. Clinical Research Funding

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

C. Funding for Travel and Other Requests

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

V. Investigator Commitment

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

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

12.2 Collection and Management of Specimens for Future Biomedical Research

1. Definitions

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

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

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

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research

The specimens collected in this trial as outlined in Section 7.1.7 Future Biomedical Research will be used to study various causes for how subjects may respond to a drug/vaccine. Future biomedical research specimen(s) will be stored to provide a resource for future trials conducted by Merck focused on the study of biomarkers responsible for how a drug/vaccine enters and is removed by the body, how a drug/vaccine works, other pathways a drug/vaccine may interact with, or other aspects of disease. The specimen(s) may be used for future assay development and/or drug/vaccine development.

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

3. Summary of Procedures for Future Biomedical Research

a. Subjects for Enrollment

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

b. Informed Consent

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

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

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

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

c. eCRF Documentation for Future Biomedical Research Specimens

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

d. Future Biomedical Research Specimen Collections

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

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

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

4. Confidential Subject Information for Future Biomedical Research

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

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

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

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

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

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

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

5. Biorepository Specimen Usage

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

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

6. Withdrawal From Future Biomedical Research

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

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

7. Retention of Specimens

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

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

8. Data Security

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

9. Reporting of Future Biomedical Research Data to Subjects

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

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

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

10. Gender, Ethnicity and Minorities

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

11. Risks Versus Benefits of Future Biomedical Research

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

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

It is necessary for subject-related data (i.e., ethnicity, diagnosis, drug therapy and dosage, age, toxicities, etc.) to be re-associated to double coded specimens at the time of data analysis. These subject data will be kept in a separate, secure Merck database, and all specimens will be stripped of subject identifiers. No information concerning results obtained from future biomedical research will be entered into clinical records, nor will it

be released to outside persons or agencies, in any way that could be tied to an individual subject.

12. Self-Reported Ethnicity

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

13. Questions

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

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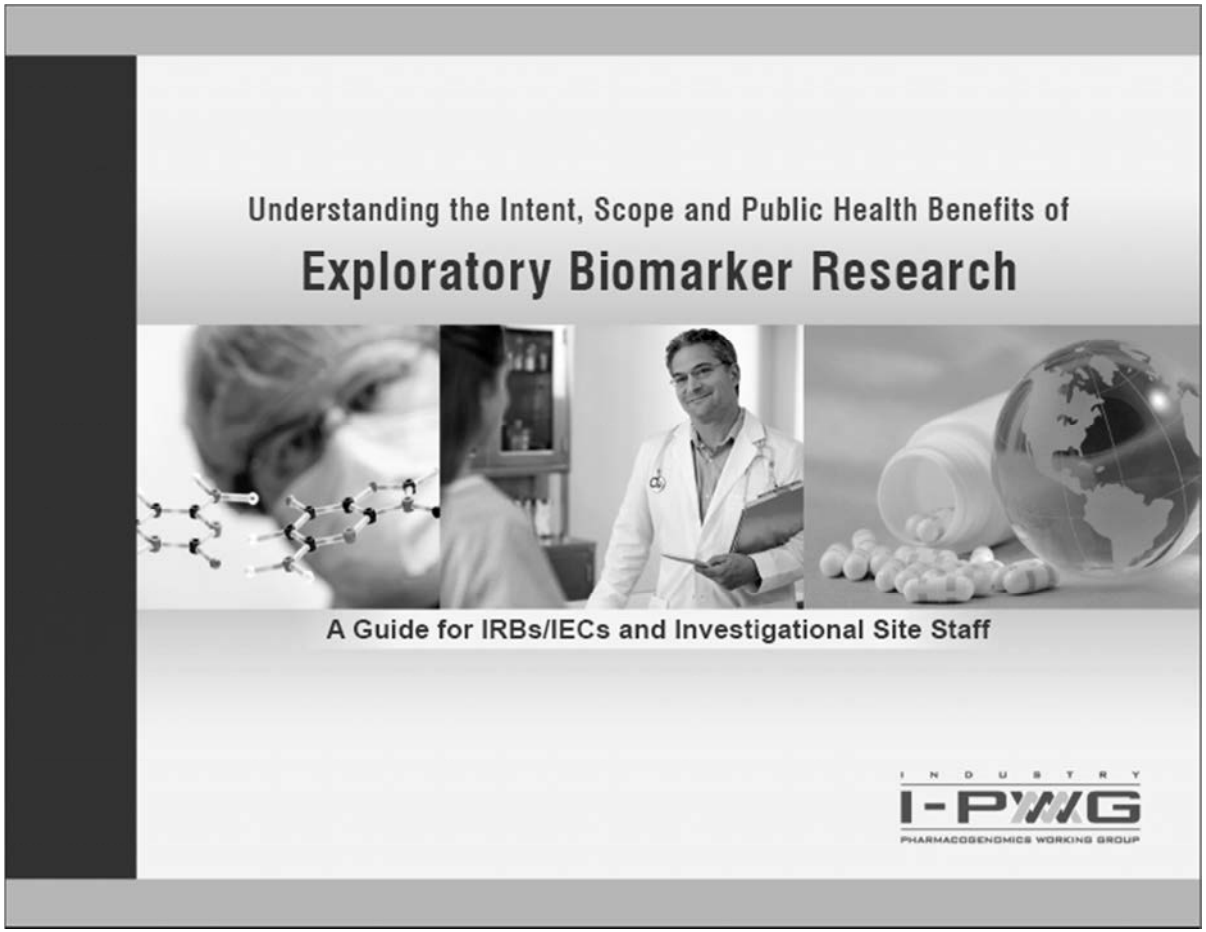
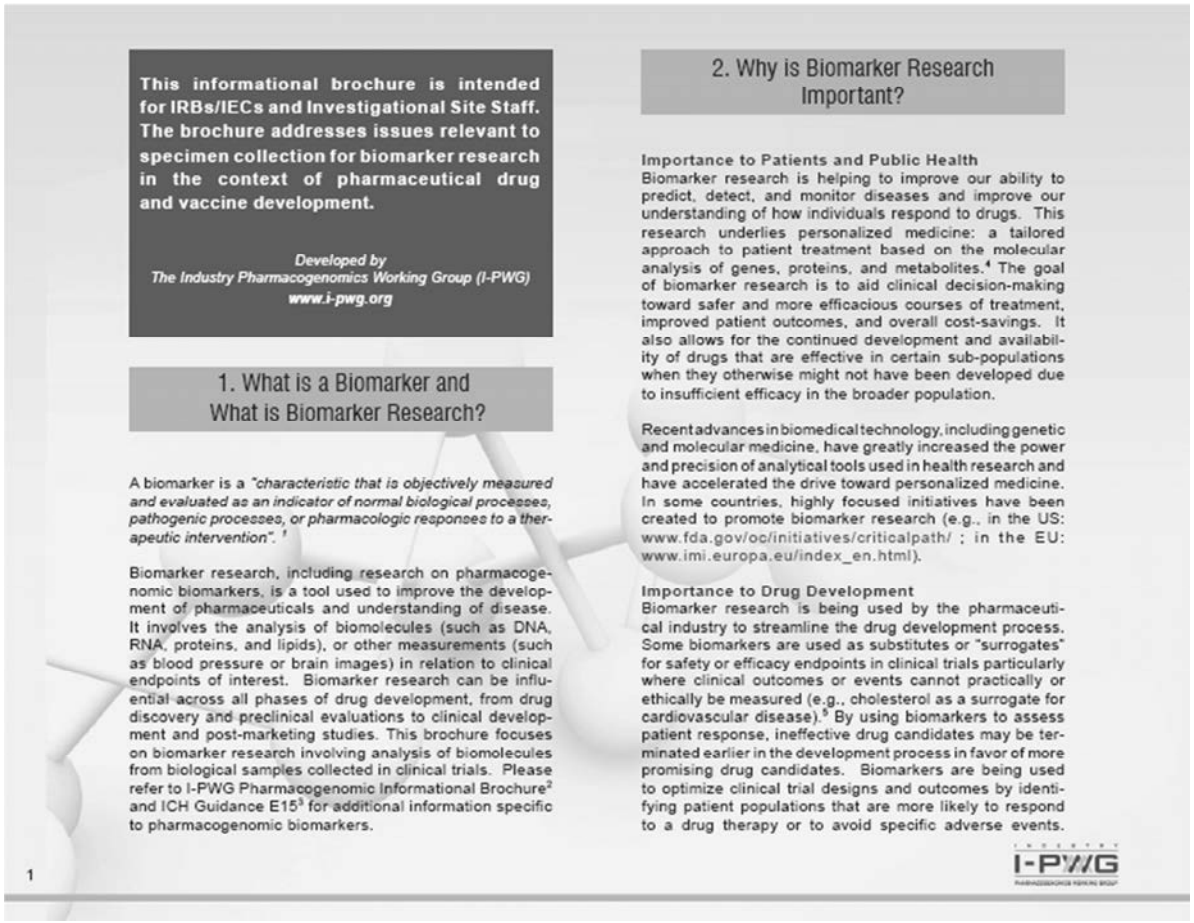
12.3 Understanding the Intent, Scope and Public Health Benefits of Exploratory Biomarker Research: A Guide for IRBs/IECs and Investigational Site Staff





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

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

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

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

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

2. Why is Biomarker Research Important?

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

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

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

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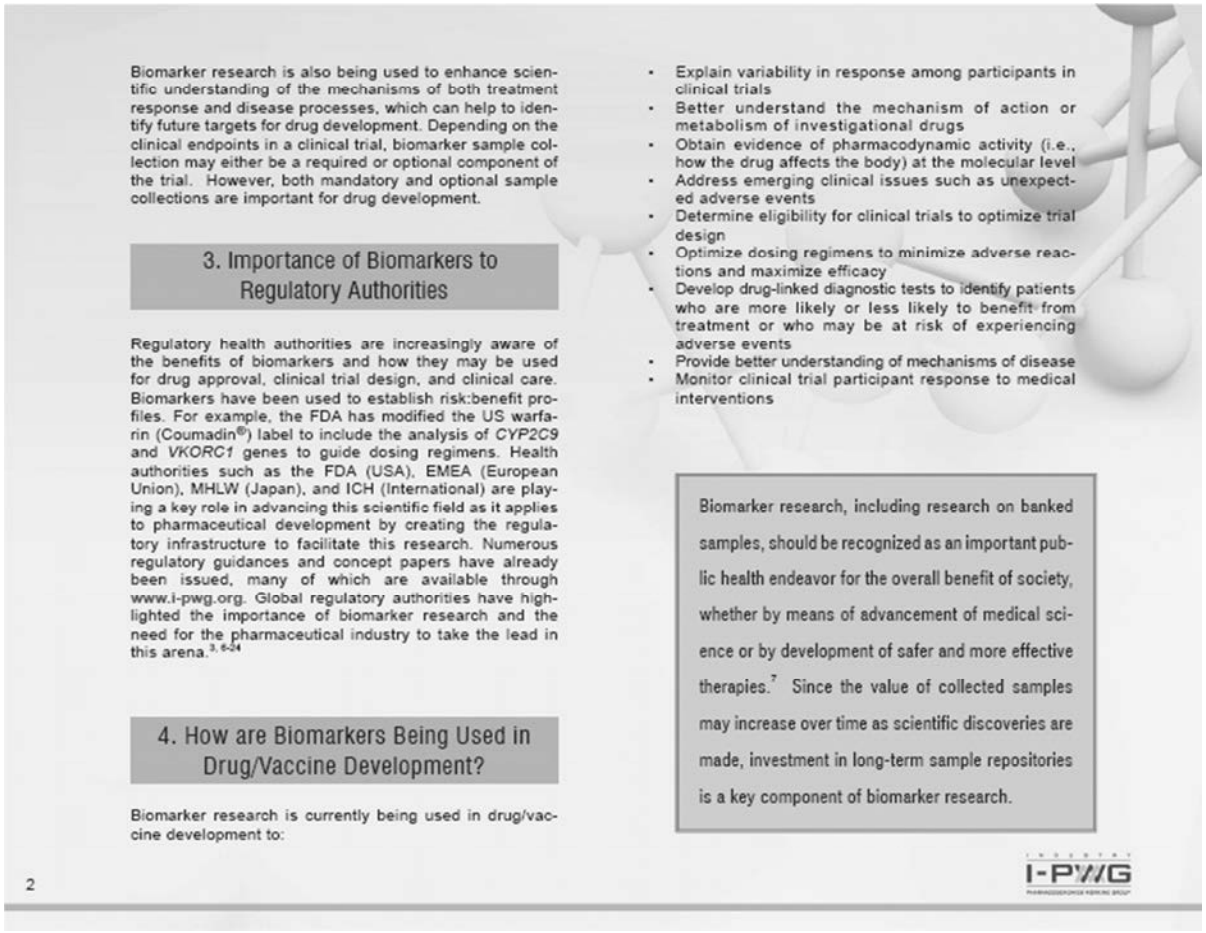
Biomarker research is also being used to enhance scientific understanding of the mechanisms of both treatment response and disease processes, which can help to identify future targets for drug development. Depending on the clinical endpoints in a clinical trial, biomarker sample collection may either be a required or optional component of the trial. However, both mandatory and optional sample collections are important for drug development.
3. Importance of Biomarkers to Regulatory Authorities
Regulatory health authorities are increasingly aware of the benefits of biomarkers and how they may be used for drug approval, clinical trial design, and clinical care. Biomarkers have been used to establish risk:benefit profiles. For example, the FDA has modified the US warfarin (Coumadin®) label to include the analysis of *CYP2C9* and *VKORC1* genes to guide dosing regimens. Health authorities such as the FDA (USA), EMEA (European Union), MHLW (Japan), and ICH (International) are playing a key role in advancing this scientific field as it applies to pharmaceutical development by creating the regulatory infrastructure to facilitate this research. Numerous regulatory guidances and concept papers have already been issued, many of which are available through www.i-pwg.org. Global regulatory authorities have highlighted the importance of biomarker research and the need for the pharmaceutical industry to take the lead in this arena.[3,6-24]
4. How are Biomarkers Being Used in Drug/Vaccine Development?
Biomarker research is currently being used in drug/vaccine development to:
• Explain variability in response among participants in clinical trials
• Better understand the mechanism of action or metabolism of investigational drugs
• Obtain evidence of pharmacodynamic activity (i.e., how the drug affects the body) at the molecular level
• Address emerging clinical issues such as unexpected adverse events
• Determine eligibility for clinical trials to optimize trial design
• Optimize dosing regimens to minimize adverse reactions and maximize efficacy
• Develop drug-linked diagnostic tests to identify patients who are more likely or less likely to benefit from treatment or who may be at risk of experiencing adverse events
• Provide better understanding of mechanisms of disease
• Monitor clinical trial participant response to medical interventions
Biomarker research, including research on banked samples, should be recognized as an important public health endeavor for the overall benefit of society, whether by means of advancement of medical science or by development of safer and more effective therapies.[7] Since the value of collected samples may increase over time as scientific discoveries are made, investment in long-term sample repositories is a key component of biomarker research.
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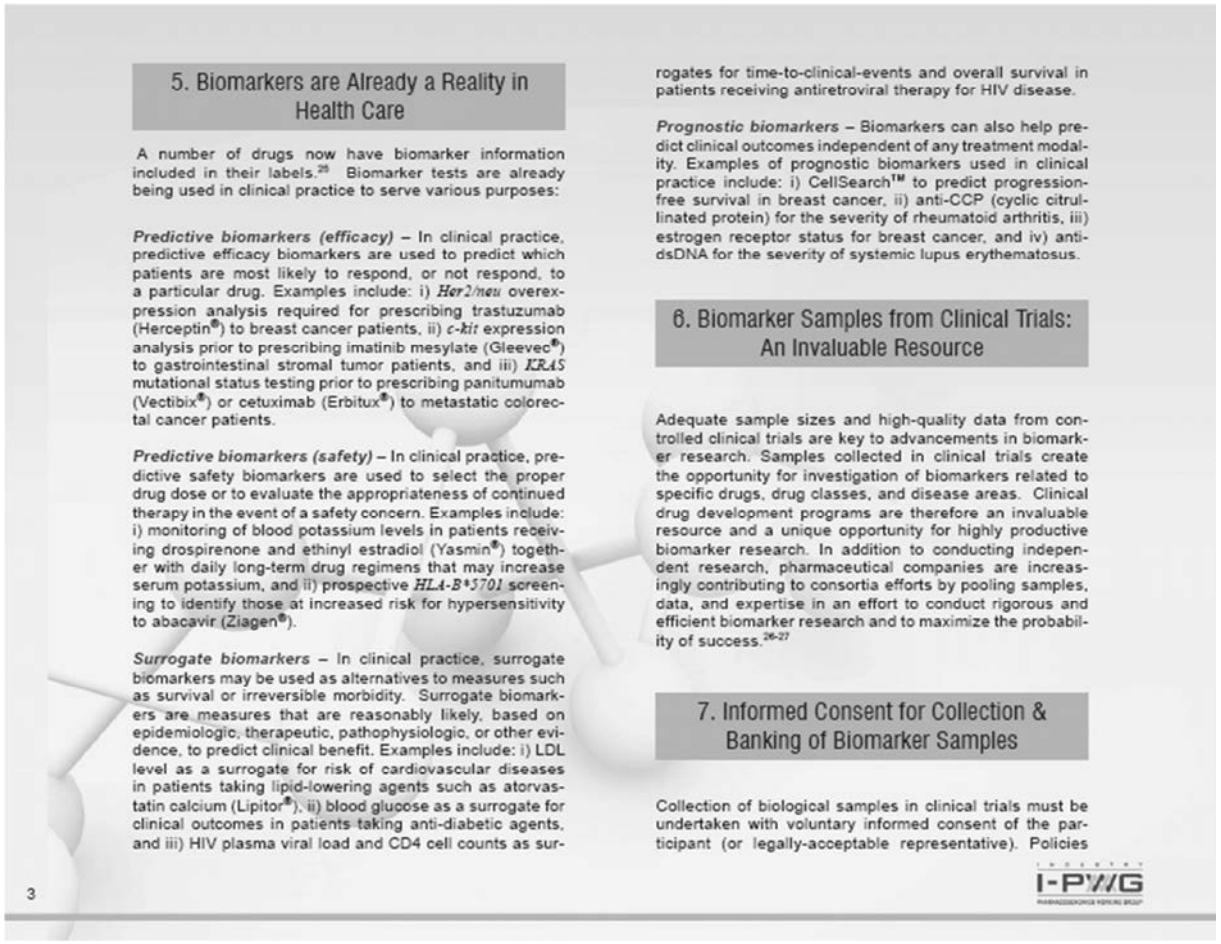

5. Biomarkers are Already a Reality in Health Care

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

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

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

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

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

6. Biomarker Samples from Clinical Trials: An Invaluable Resource

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

7. Informed Consent for Collection & Banking of Biomarker Samples

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

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

Optional vs. Required Subject Participation

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

Consent for Future Research Use

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

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

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

Withdrawal of consent / sample destruction – The informed consent form should inform participants of their right to withdraw their consent / request destruction of their samples. This should include the mechanisms for exercising that right and any limitations to exercising that right. For example, participants should be informed that it is not possible to destroy samples that have been anonymized.[3] In addition, according to industry standards and regulatory guidance, participants should be informed that data already generated prior to a consent withdrawal request are to be maintained as part of the study data.[28]

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

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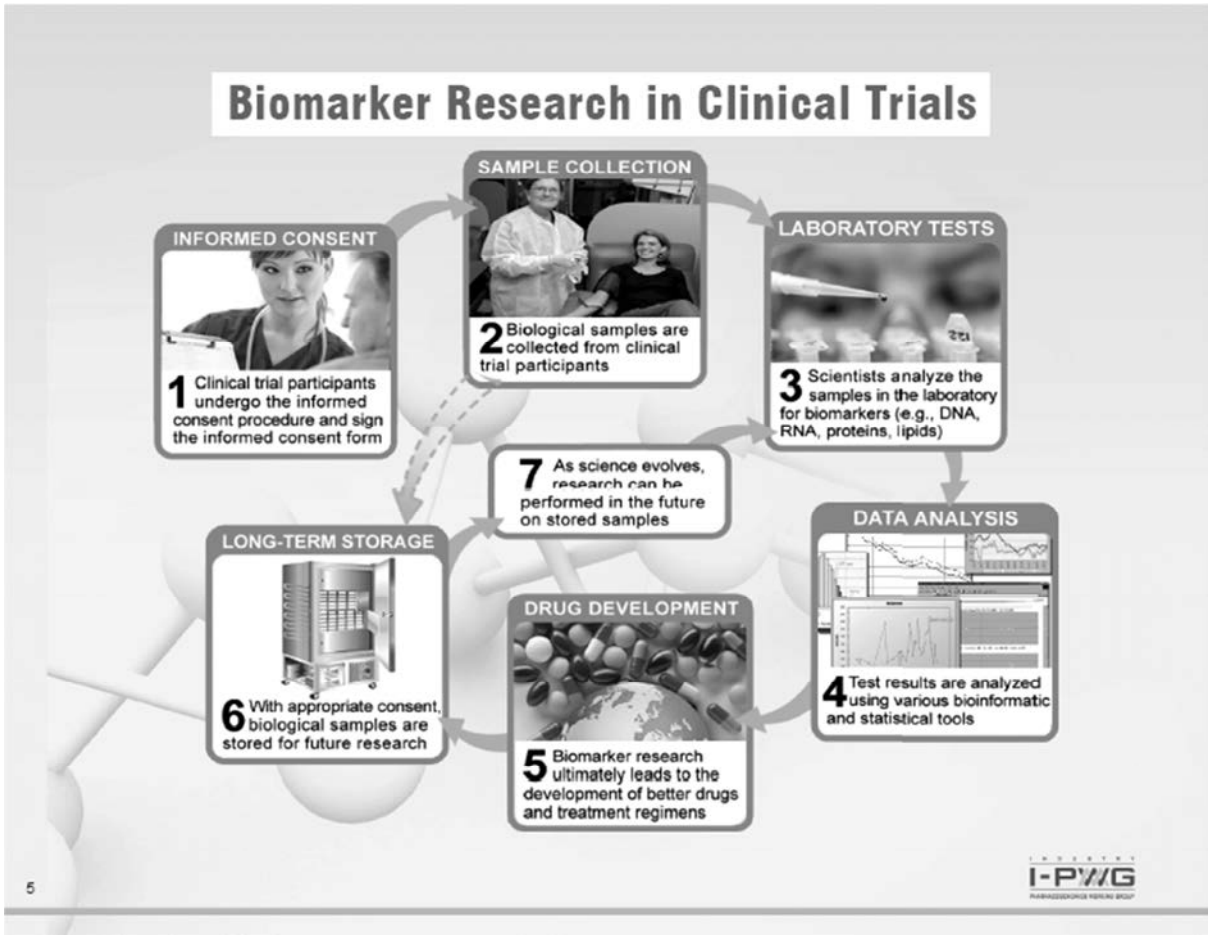
Biomarker Research in Clinical Trials
SAMPLE COLLECTION
2 Biological samples are collected from clinical trial participants
INFORMED CONSENT
1 Clinical trial participants undergo the informed consent procedure and sign the informed consent form
LABORATORY TESTS
3 Scientists analyze the samples in the laboratory for biomarkers (e.g., DNA, RNA, proteins, lipids)
7 As science evolves, research can be performed in the future on stored samples
DATA ANALYSIS
4 Test results are analyzed using various bioinformatic and statistical tools
LONG-TERM STORAGE
6 With appropriate consent, biological samples are stored for future research
DRUG DEVELOPMENT
5 Biomarker research ultimately leads to the development of better drugs and treatment regimens
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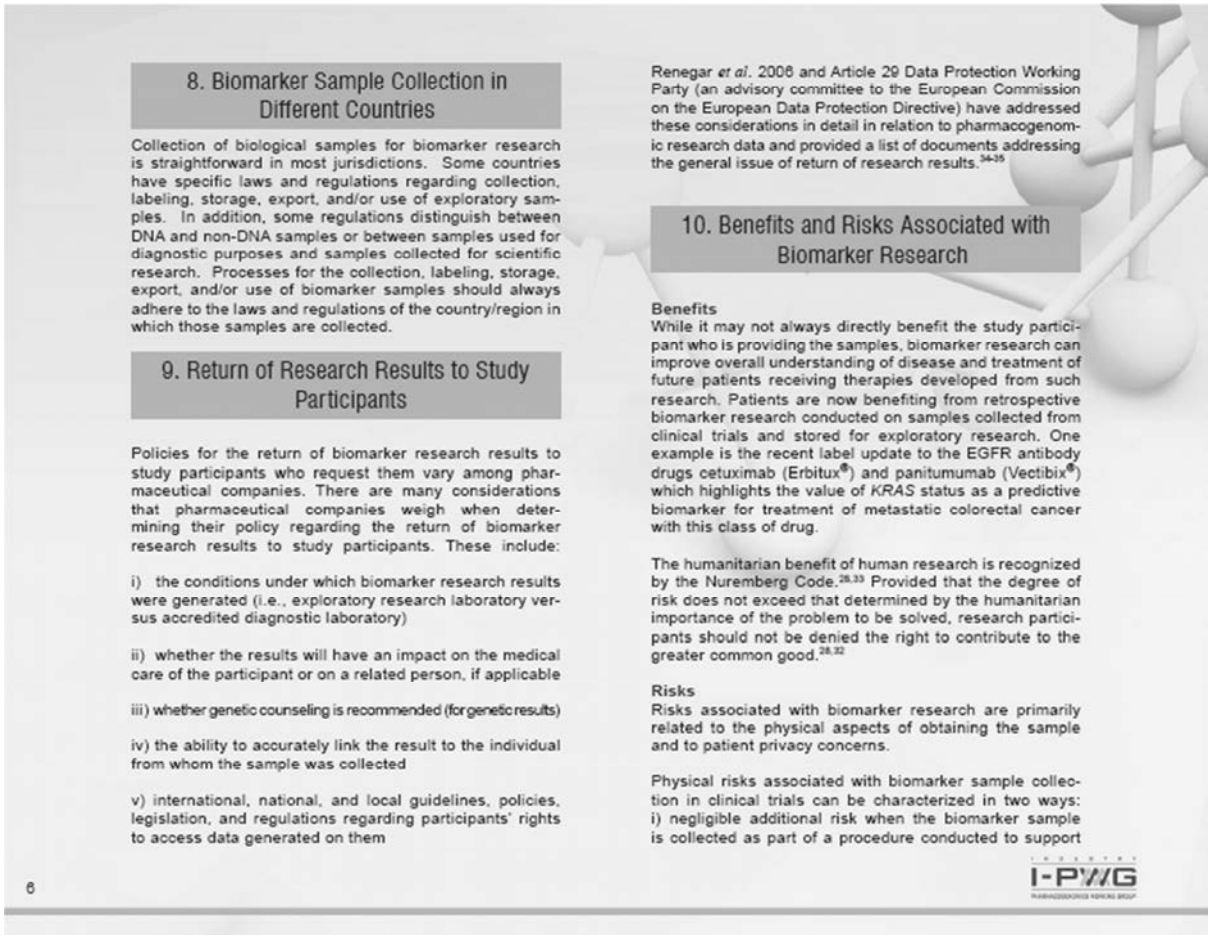

8. Biomarker Sample Collection in Different Countries

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

9. Return of Research Results to Study Participants

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

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

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

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

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

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

Renegar *et al*. 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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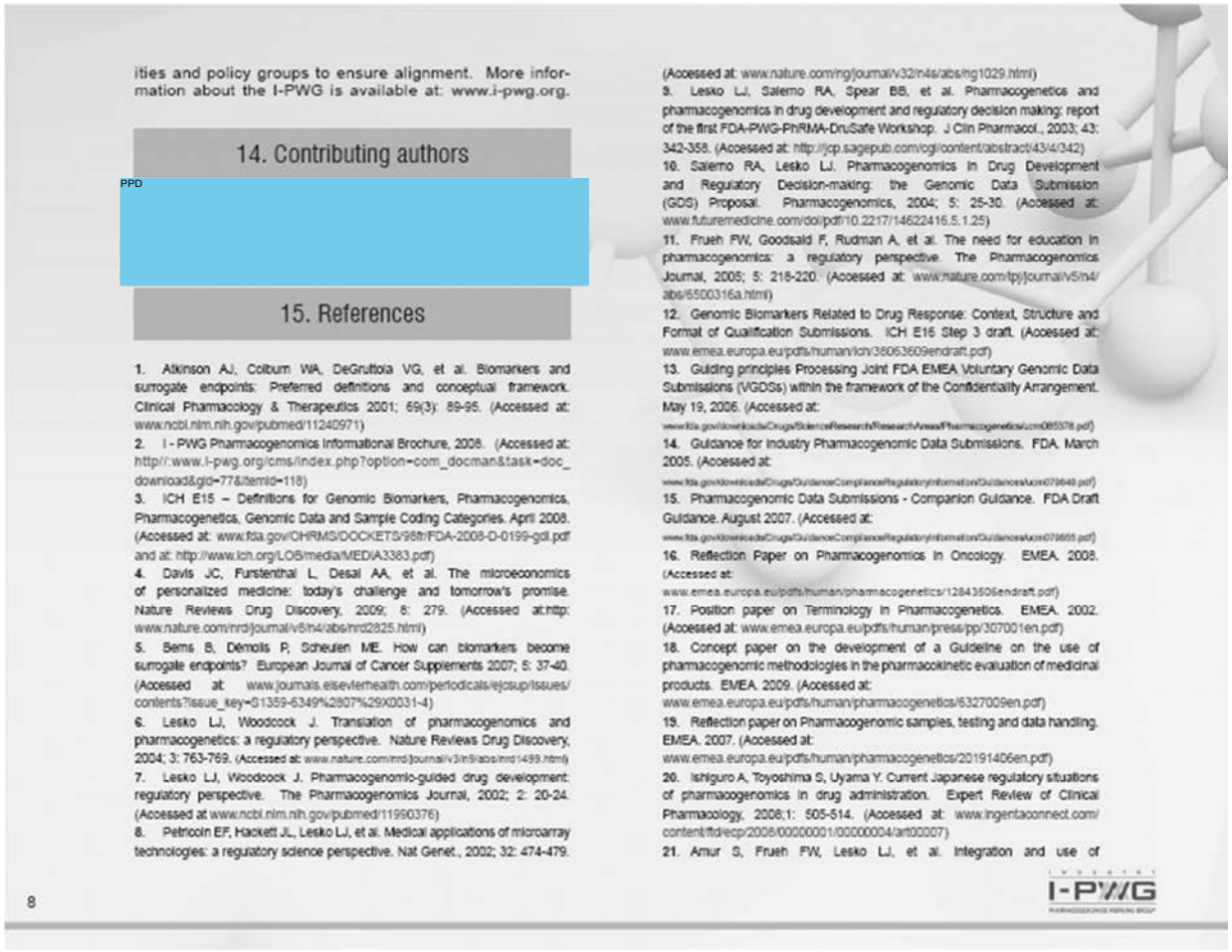

ities and policy groups to ensure alignment. More information about the I-PWG is available at: www.i-pwg.org.

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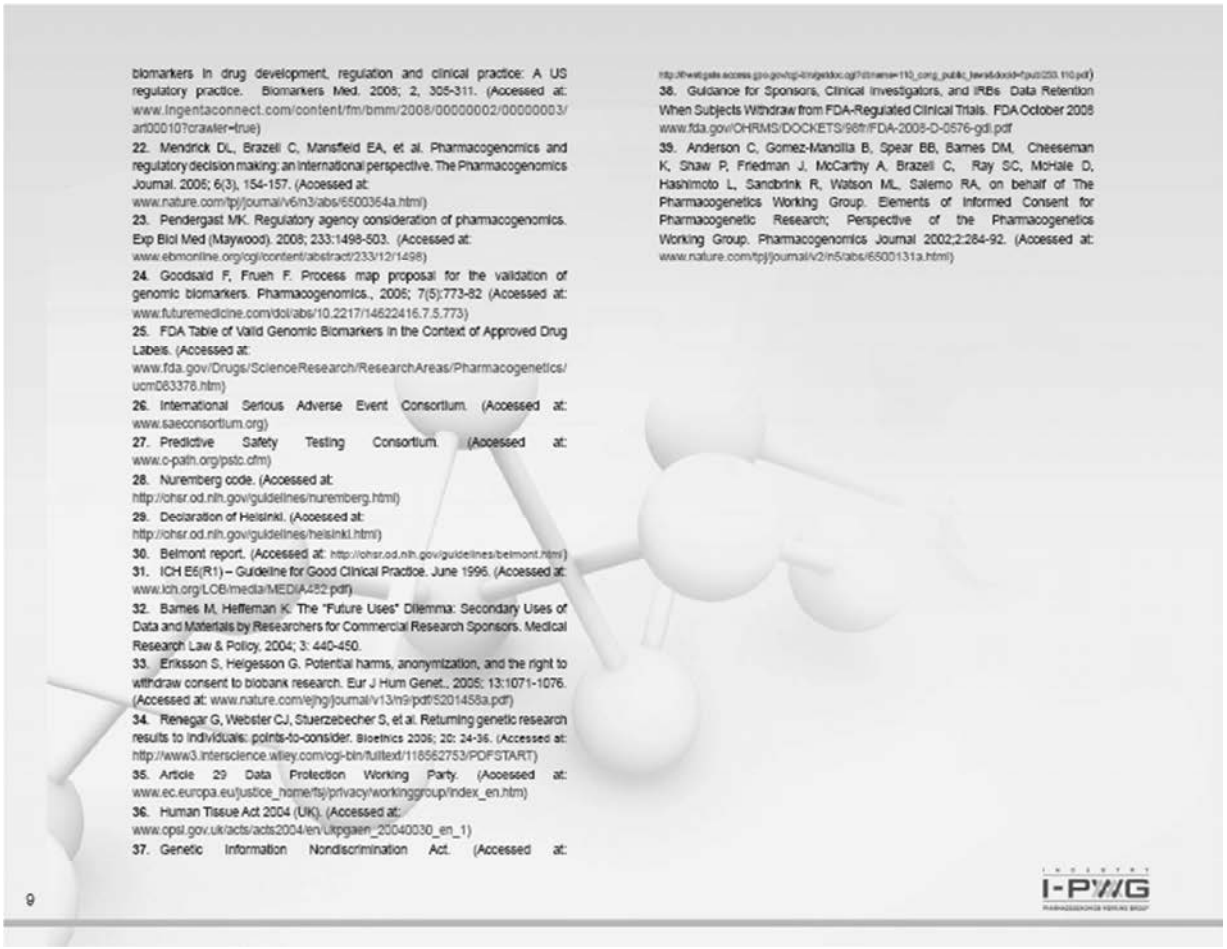

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12.4 Abbreviations

Abbreviation/Term	Definition
AE	Adverse Event
ADL	Activities of Daily Living
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
aPTT	Activated Partial Thromboplastin Time
ASaT	All Subjects as Treated
ASCO	American Society of Clinical Oncology
BCG	Bacillus of Calmette and Geurin (tuberculosis vaccine)
ß-HCG	Beta Human Chorionic Gonadotropin
BMx	Biomarker
CFR	Code of Federal Regulations
CI	Confidence Interval
CNS	Central Nervous System
CO^2	Carbon Dioxide
COPD	Chronic Obstructive Pulmonary Disease
CR	Complete Response
CRF	Case Report Form
CRC	Colorectal Carcinoma
CrCl	Calculated Creatinine Clearance
CSR	Clinical Study Report
CT	Computed Tomography
CTCAE	Common Toxicity Criteria for Adverse Events
CTFG	Clinical Trials Facilitation Group
CTLA-4	Cytotoxic T-Lymphocyte-Associated Antigen-4
DKA	Diabetic Ketoacidosis
DNA	Deoxyribonucleic acid
DOR	Duration of Response
ECI	Events of Clinical Interest
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EOC	Executive Oversight Committee
ERC	Ethics Review Committee
FBR	Future Biomedical Research
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FDAMA	Food and Drug Administration Modernization Act
FFPE	Formalin-Fixed Paraffin-Embedded
FNA	Fine Needle Aspirate
FT4	Free Thyroxine
GBM	Glioblastoma multiforme
GCP	Good Clinical Practice
GEP	Gene Expression Profile
GFR	Glomerular Filtration Rate
HBsAg	Hepatitis B Surface Antigen
HCV	Hepatitis C Virus
Hgb	Hemoglobin
HIV	Human Immunodeficiency Virus
IB	Investigator's Brochure
ICH	International Conference on Harmonization

Abbreviation/Term	Definition
IEC	Internal Ethics Committee
IHC	Immunohistochemistry
INR	International Normalized Ratio
IRB	Institutional Review Board
irRECIST	Immune-related RECIST
ITIM	Immunoreceptor Tyrosine-based Inhibition Motif
ITSM	Immunoreceptor Tyrosine-based Switch Motif
IV	Intravenous
IVRS	Interactive Voice Response System
IWRS	Integrated Web Response System
KM	Kaplan-Meier
KN	KEYNOTE
LDH	Lactate Dehydrogenase
mAb	Monoclonal Antibody
Mg	Milligram
MRI	Magnetic Resonance Imaging
MSD	Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
MSI	Microsatellite Instability
MSI-H	MSI-high
MSS	Microsatellite Stable
N/A	Not Applicable
NCI	National Cancer Institute
NSAID	Non-steroidal Anti-inflammatory Drug
NSCLC	Non-small Cell Lung Cancer
NPV	Negative Predictive Value

Abbreviation/Term	Definition
ORR	Objective Response Rate
OS	Overall Survival
OTC	Over-the-counter
PD	Pharmacodynamic or Progressive Disease
PD-1	Programmed Cell Death 1
PD-L1	Programmed Death Ligand 1
PD-L2	Programmed Death Ligand 2
PFS	Progression Free Survival
PGt	Pharmacogenetic
PI	Principal Investigator
PIN	Personal Identification Number
PK	Pharmacokinetic
PPV	Positive Predictive Value
PR	Partial Response
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
Q2W	Every 2 weeks
Q3W	Every 3 weeks
RBC	Red Blood Cell Count
RECIST	Response Evaluation Criteria in Solid Tumors
RECIST 1.1	RECIST, version 1.1
RNA	Ribonucleic Acid
RR	Response Rate
SAE	Serious Adverse Event
sSAP	Supplemental Statistical Analysis Plan
SD	Stable Disease
SEER	Surveillance, Epidemiology, and End Results
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SOC	Standard of Care
SOP	Standard Operating Procedures
sPD-L1	Soluble PD-L1
T1DM	Type 1 Diabetes Mellitus
T3	Triiodothyronine
TAM	Tumor Associated Macrophage
TIL	Tumor Infiltrating Lymphocyte
TPS	Tumor Proportion Score
TSH	Thyroid Stimulating Hormone
UK	United Kingdom
ULN	Upper Limit of Normal
V-type	Variable-type
WBC	White Blood Cell Count
WES	Whole Exome Sequencing
WHO	World Health Organization

12.5 Eastern Cooperative Oncology Group 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.

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

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

12.7 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 trial 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 trial.

* As published in the European Journal of Cancer:

E.A. Eisenhauer, P. Therasse, J. Bogaerts, L.H. Schwartz, D. Sargent, R. Ford, J. Dancey, S. Arbuck, S. Gwyther, M. Mooney, L. Rubinstein, L. Shankar, L. Dodd, R. Kaplan, D. Lacombe, J. Verweij. New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009 Jan;45(2):228-47.

12.8 Approximate Blood/Tissue Volumes Drawn/Collected by Trial Visit and by Sample Types

12.8.1 Initial Course:

Test	Total amount of draw	Sample type		Cycle	Screen	1	2	3	4	5	6	7	8	9	10	11	12	13 and beyond	Discon	Safety Follow up- 30 Days	3 Mo (Follow up 1)	Every 12 weeks after Discon (FU2 and beyond)	Survival f/u: Every 12 weeks
Pregnancy Test (Serum or Urine)	5	serum			5.0																		
PT/INR and aPTT	4.5	plasma			4.5																		
CBC with differential	3	whole blood			3.0		3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0			
Comprehensive Chemistry Profile	5	serum			5.0		5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0			
T3, FT4, and TSH	4	serum			4.0		4.0		4.0		4.0		4.0		4.0		4.0			4.0			
Pharmacokinetics	3.5	serum				3.5			3.5														
Blood for serum biomarkers	4	serum				4.0																	
Blood for Plasma biomarkers	6	plasma	-			6.0																	
Blood for genetics	8.5	whole blood				8.5																	
Blood for correlative studies collection - DNA	2					2.0	2.0	2.0											2.0				
Blood for correlative studies collection - RNA	2.5	whole blood				2.5	2.5	2.5											2.5				
Archival Tissue	tissue	FFPET			X																		
Fresh Tumor Tissue (CNB)	tissue	CNB or excisional			X																		
One Lavendar EDTA for MSI	6	whole blood			6.0																		
TOTALS					**27.5**	**26.5**	**17**	**13**	**16**	**8**	**12**	**8**	**12**	**8**	**12**	**8**	**12**	**8**	**12.5**	**12**	**0**	**0**	**0**
5 mls of blood= 1 teaspoon of																							
15 mls of blood= 1 tablespoon of blood																							

12.8.2 Second Course:

Test	Second course (SC) SC1	SC2	SC3	SC4	SC5	SC6	SC7	SC8	SC9	SC10	SC11	SC12	SC13	Discon SC	Safety Follow Up 30 Days	3 Months	6 Months	Every 3 months after Month 6	Survival f/u: Every 2 months
Pregnancy Test (Serum or Urine)	5.0																		
PT/INR and aPTT																			
CBC with differential	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0				
Comprehensive Chemistry Profile	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0				
T3, FT4, and TSH	4.0	4.0		4.0		4.0		4.0		4.0		4.0			4.0				
Pharmacokinetics																			
Blood for serum biomarkers																			
Blood for Plasma biomarkers																			
Blood for genetics																			
Blood for correlative studies collection - DNA	2.0	2.0	2.0											2.0					
Blood for correlative studies collection - RNA	2.5	2.5	2.5											2.5					
Archival Tissue																			
Fresh Tumor Tissue (CNB)	X																		
One Lavendar EDTA for MSI																			
TOTALS	**21.5**	**16.5**	**13**	**12**	**8**	**12**	**8**	**12**	**8**	**12**	**8**	**12**	**8**	**12.5**	**12**	**0**	**0**	**0**	**0**
5 mls of blood= 1 teaspoon of																			
15 mls of blood= 1 tablespoon of blood																			

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 7.2 – 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	