Official Protocol Title:	A Phase II Clinical Trial of Single Agent Pembrolizumab (MK-3475) in Subjects with Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma (HNSCC) Who Have Failed Platinum and Cetuximab
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TITLE:

A Phase II Clinical Trial of Single Agent Pembrolizumab (MK-3475) in Subjects with Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma (HNSCC) Who Have Failed Platinum and Cetuximab

IND NUMBER: 122,325
EudraCT NUMBER: 2014-002447-18

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SUMMARY OF CHANGES

PRIMARY REASON(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
Change from Amendment 055-04 to 055-05			
2.2	Trial Diagram	The trial diagram adding pembrolizumab extension trial after survival follow-up was replaced with the correct trial diagram.	Correction.
Changes from Amendment 055-03 to 055-05			
6.1	Initial Treatment Phase and Second Course Phase (Retreatment)	Survival status activities are shown taking place throughout the trial. The frequency of telephone contacts during the survival follow-up phase was changed from every 12 weeks to approximately every 12 weeks.	This change enables flexibility of survival status activities, to ensure that current, complete survival data are available at the time of database locks. To enable flexibility of survival status activities
7.1.5.3.3	Survival Follow-Up	The frequency of telephone contacts during the survival follow-up phase was changed from every 12 weeks to approximately 12 weeks.	To enable flexibility of survival status activities.
7.1.5.4	Survival Status	This section was added to state that the Sponsor may request updated survival data during the course of the study.	To ensure that current and complete survival data are available at the time of database locks

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
5.2.1.2	Dose Modification (Escalation/Titration/Other)	The dose modification guidelines were replaced; the replacement guidelines identify specific immune-related adverse events associated with pembrolizumab.	To provide current comprehensive guidelines for management of immune related adverse events.

ADDITIONAL CHANGE(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
Change from Amendment 055-04 to 055-05			
12.4	Abbreviations	The definition of ORR was changed from overall response rate to objective response rate.	Correction.
Changes from Amendment 055-03 to 055-05			
1.0	Trial Summary	Once subjects have achieved the trial objective or the trial has ended, subjects are discontinued from this trial and will be enrolled in an extension trial to continue protocol-defined assessments and treatment.	This trial has been identified to roll over into an extension trial.
2.2	Trial Diagram	The pembrolizumab extension trial after survival follow-up is added.	
5.10	Beginning and End of the Trial	Upon trial completion, subjects are discontinued and enrolled in a pembrolizumab extension trial.	

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
6.1	Initial Treatment Phase and Second Course Phase (Retreatment)	Collection of 30-day and 3-month follow-up samples for pharmacokinetics and anti-drug antibodies was removed.	Based on data collected from other pembrolizumab trials, it is no longer necessary to collect these samples.
6.1	Initial Treatment Phase and Second Course Phase (Retreatment)	Text was added to allow flexibility around the imaging schedule for subjects in follow-up.	To maintain subject retention and the collection of survival status for every subject enrolled.
7.1.2.6.3	Assessment of Disease		
7.1.5.3.2	Follow-up Visits		
7.1.3.2	Pharmacokinetic/ Pharmacodynamic Evaluations	Blood samples collected for pharmacokinetics and anti-drug antibodies may be only stored, and further analysis may be performed if required. Sections 7.1.3.2.1 and 7.1.3.2.2 were previously in the protocol.	These changes were made to clarify that samples collected may be stored and to allow flexibility for the continuation of their collection.
8.2.5.3.2	Pharmacokinetic Analysis	This analysis, if performed, will be reported separately.	This is added to make clear that if PK analysis is performed, it will be reported in a stand-alone report.
4.1.2	Pre-clinical and Clinical Trials	Reference 29 is renumbered 28.	Reference 29 precedes reference 28 in previous protocol versions.
4.1.3	Ongoing Clinical Trials	Reference 28 is renumbered 29.	Sequence of references
		Reference 42 is removed.	This publication refers to quality of life assessment and not to radiologic response.
4.2.2.1	Efficacy Endpoints	Reference 32 is renumbered 31.	Sequence of references

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
8.2.7	Sample Size and Power Calculations	Reference 29 is renumbered 28.	Sequence of references
11.0	List of References	References 29, 28, and 32 are renumbered 28, 29, and 31.	Sequence of references
		Reference 30 is corrected.	Incorrect reference in previous protocol versions
		References 31, 33 to 41, and 43 to 49 in previous protocol versions are removed.	These references are not cited in the text.
12.4	Abbreviations	eCRF (electronic Case Report Form) is added. ORST (Oncologic Response-Solid Tumor) is defined.	This abbreviation had not been in Section 12.4. This abbreviation had not been defined in the text.

No additional changes.

1.0 TRIAL SUMMARY

Abbreviated Title	Ph II Clinical Trial of Pembrolizumab (MK-3475) in Subjects with Refractory HNSCC
Trial Phase	II
Clinical Indication	Head and Neck Squamous Cell Carcinoma (HNSCC)
Trial Type	Interventional
Type of control	No Treatment Control
Route of administration	Intravenous
Trial Blinding	Unblinded Open-label
(Select Groups)	Pembrolizumab (MK-3475) 200 mg every 3 weeks (Q3W)
Number of trial subjects	Approximately 150 subjects will be enrolled.
Estimated duration of trial	The sponsor estimates that the trial will require approximately 36 months from the time the first subject signs the informed consent until the last subject's last visit.
Duration of Participation	Each subject will participate in the trial from the time the subject signs the Informed Consent Form (ICF) through the final protocol-specified contact. After a screening phase of 28 days, eligible subjects will receive treatment on Day 1 of each 3-week dosing cycle. Treatment with pembrolizumab (MK-3475) will continue until documented confirmed disease progression, unacceptable adverse event(s), intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw the subject, subject withdraws consent, pregnancy of the patient, noncompliance with trial treatment or procedure requirements, subject receives 24 months of study medication, or administrative reasons. After the end of treatment, each patient will be followed for 30 days for adverse event monitoring (serious adverse events will be collected for 90 days after the end of treatment or 30 days after the end of treatment if the patient initiates new anticancer therapy, whichever is earlier). Subjects who discontinue for reasons other than radiographic disease progression will have post-treatment follow-up for disease status until end of study, disease progression, initiating a non-study cancer treatment, withdrawing consent, or becoming lost to follow-up. All subjects will be followed by telephone for overall survival until death, withdrawal of consent, or the Investigator is notified by the Sponsor to discontinue follow-up. Once subjects have achieved the trial objective or the trial has ended, subjects are discontinued from this trial and will be enrolled in an extension trial to continue protocol-defined assessments and treatment.

A list of abbreviations used in this document can be found in Section 12.5.

2.0 TRIAL DESIGN

2.1 Trial Design

This is a multicenter, nonrandomized, single-cohort trial of pembrolizumab (MK-3475) in subjects with recurrent and/or metastatic head and neck squamous cell carcinoma who have progressed on platinum and cetuximab therapy. Approximately 150 subjects are planned to be enrolled in this trial to examine the safety and efficacy of pembrolizumab (MK-3475) in this patient population. Subjects will receive 200 mg of pembrolizumab (MK-3475) administered every 3 weeks (Q3W). Subjects will be evaluated every 6-9 weeks with radiographic imaging to assess response to treatment. RECIST 1.1 response rate as assessed by the central vendor will be used as the primary efficacy endpoint. RECIST 1.1 will be adapted as described in Section 4.2.3.1 to accommodate for the tumor response patterns seen with pembrolizumab (MK-3475) treatment (e.g., tumor flare), and this adapted RECIST will be used as determined by site assessment for treatment decisions. Adverse events will be monitored throughout the trial and graded in severity according to the guidelines outlined in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Treatment with pembrolizumab (MK-3475) will continue until documented disease progression, unacceptable adverse event(s), intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw the subject, subject withdraws consent, pregnancy of the subject, noncompliance with trial treatment or procedure requirements, completion of 24 months of treatment with pembrolizumab (MK-3475), or administrative reasons. Subjects who attain an investigator-determined confirmed complete response (CR) may consider stopping trial treatment after receiving at least 24 weeks of treatment. Subjects who discontinue after at least 24 months of therapy for reasons other than disease progression or intolerability or who discontinue after attaining a CR may be eligible for up to one year of retreatment after they have experienced radiographic disease progression. The decision to retreat will be at the discretion of the investigator only if no cancer treatment was administered since the last dose of pembrolizumab (MK-3475), the subject still meets the safety parameters listed in the Inclusion/Exclusion criteria and the trial remains open (refer to Section 7.1.5.2.1 for further details). After the end of treatment, each subject will be followed for 30 days for adverse event monitoring (serious adverse events and events of clinical interest will be collected for 90 days after the end of treatment or 30 days after the end of treatment if the subject initiates new anticancer therapy, whichever is earlier). Subjects who discontinue treatment for reasons other than disease progression will have post-treatment follow-up for disease status until disease progression, initiating a non-study cancer treatment, withdrawing consent, or becoming lost to follow-up. All subjects will be followed by telephone contact for overall survival until death, withdrawal of consent or the Investigator is notified by the Sponsor to discontinue follow-up, whichever comes first.

The primary objectives of the trial are to determine the safety and tolerability of the 200 mg Q3W dose of pembrolizumab (MK-3475), and to determine the anti-tumor activity of pembrolizumab (MK-3475) in all subjects and in subjects with PD-L1 strong positive recurrent and/or metastatic head and neck squamous cell carcinoma (HNSCC) receiving 200 mg Q3W dose. Secondary objectives include progression-free survival (PFS), overall survival (OS) and response duration (DOR). In addition, the anti-tumor activity of

pembrolizumab (MK-3475) in subjects with human papillomavirus (HPV) positive head/neck cancer will be evaluated as a secondary objective. The relationship between candidate efficacy/resistance biomarkers (including PD-L1 expression in the tumor and its microenvironment) and anti-tumor activity of pembrolizumab (MK-3475) will be investigated as an exploratory objective.

Although subjects will be enrolled regardless of PD-L1 status, subjects will be required to provide tissue of a tumor lesion to be evaluated at a central laboratory for expression status of PD-L1 by immunohistochemistry (IHC).

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

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

2.2 Trial Diagram

The trial design is depicted in Figure 1.

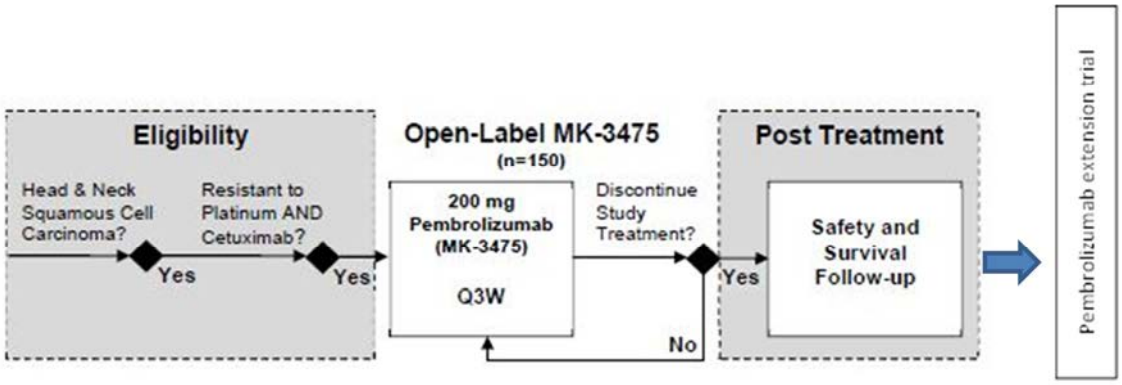

Figure 1 Trial Design

3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

3.1 Primary Objective(s) & Hypothesis(es)

1) **Objective:** To determine the safety and tolerability of 200 mg Q3W dose of pembrolizumab (MK-3475) in subjects with recurrent and/or metastatic head and neck squamous cell carcinoma who have progressed on platinum and cetuximab therapy.

2) **Objective:** To evaluate anti-tumor activity of pembrolizumab (MK-3475) by objective response rate (ORR) using RECIST 1.1 assessed by independent radiology review in subjects with recurrent and/or metastatic head and neck squamous cell carcinoma who have progressed on platinum and cetuximab therapy.

   Hypothesis: Intravenous administration of single agent pembrolizumab (MK-3475) to subjects with recurrent and/or metastatic head and neck squamous cell carcinoma who have progressed on platinum and cetuximab therapy will result in a clinically meaningful ORR of greater than 5% based on RECIST 1.1 by independent radiology review.

3) **Objective:** To evaluate anti-tumor activity of pembrolizumab (MK-3475) by ORR using RECIST 1.1 assessed by independent radiology review in subjects with PD-L1 strong positive recurrent and/or metastatic head and neck squamous cell carcinoma who have progressed on platinum and cetuximab therapy.

   Hypothesis: Intravenous administration of single agent pembrolizumab (MK-3475) to subjects with PD-L1 strong positive recurrent and/or metastatic head and neck squamous cell carcinoma who have progressed on platinum and cetuximab therapy will result in a clinically meaningful ORR of greater than 5% based on RECIST 1.1 by independent radiology review.

The study can be declared successful in the respective population or subpopulation if *either* the hypothesis test for objective (2) or the hypothesis test for objective (3) is significant.

3.2 Secondary Objective(s) & Hypothesis(es)

1) **Objective:** To evaluate anti-tumor activity of pembrolizumab (MK-3475) by ORR using RECIST 1.1 assessed by independent radiology review in subjects with PD-L1 positive recurrent and/or metastatic head and neck squamous cell carcinoma who have progressed on platinum and cetuximab therapy.

   Hypothesis: Intravenous administration of single agent pembrolizumab (MK-3475) to subjects with PD-L1 positive recurrent and/or metastatic head and neck squamous cell carcinoma who have progressed on platinum and cetuximab therapy will result in a clinically meaningful ORR of greater than 5% based on RECIST 1.1.

2) **Objective**: To estimate the response duration based on RECIST 1.1 by independent radiology review in all subjects receiving pembrolizumab (MK-3475) with recurrent and/or metastatic head and neck squamous cell carcinoma who have progressed on platinum and cetuximab therapy.

3) **Objective**: To estimate the response duration based on RECIST 1.1 by independent radiology review separately in PD-L1 strong positive subjects and in PD-L1 positive subjects receiving pembrolizumab (MK-3475) with recurrent and/or metastatic head and neck squamous cell carcinoma who have progressed on platinum and cetuximab therapy.

4) **Objective**: To estimate anti-tumor activity separately in all subjects, in PD-L1 strong positive subjects, and in PD-L1 and all PD-L1 positive subjects receiving pembrolizumab (MK-3475) by objective response rate (ORR) using modified RECIST 1.1 by independent radiology review in subjects with recurrent and/or metastatic head and neck squamous cell carcinoma who have progressed on platinum and cetuximab therapy.

5) **Objective**: To estimate the anti-tumor activity of pembrolizumab (MK-3475) by ORR using RECIST 1.1 by independent radiology review in all subjects with HPV positive recurrent and/or metastatic head and neck squamous cell carcinoma who have progressed on platinum and cetuximab therapy.

6) **Objective**: To estimate the progression-free survival (PFS) using RECIST 1.1 by independent radiology review separately in all subjects, in PD-L1 strong positive subjects, and in all PD-L1 positive subjects receiving pembrolizumab (MK-3475) with recurrent and/or metastatic head and neck squamous cell carcinoma who have progressed on platinum and cetuximab therapy.

7) **Objective**: To estimate the overall survival (OS) separately in all subjects, in PD-L1 strong positive subjects, and in all PD-L1 positive subjects receiving pembrolizumab (MK-3475) with recurrent and/or metastatic head and neck squamous cell carcinoma who have progressed on platinum and cetuximab therapy.

3.3 Exploratory Objectives

1) **Objective**: To estimate the progression-free survival (PFS) using modified RECIST 1.1 by independent radiology review in subjects receiving pembrolizumab (MK-3475) with recurrent and/or metastatic head and neck squamous cell carcinoma who have progressed on platinum and cetuximab therapy.

2) **Objective**: To estimate ORR using RECIST 1.1 assessed by independent radiology review in subjects with PD-L1 combined positive score ≥ 1% recurrent and/or metastatic head and neck squamous cell carcinoma who have progressed on platinum and cetuximab therapy.

3) **Objective**: To investigate the relationship between candidate efficacy/resistance biomarkers and anti-tumor activity of pembrolizumab (MK-3475) utilizing pre-treatment tumor biopsies and blood sampling.

4.0 BACKGROUND & RATIONALE

4.1 Background

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

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an Ig superfamily member related to CD28 and CTLA-4 which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) [7; 8]. The structure of murine PD-1 has been resolved [9]. PD-1 and family members are type I transmembrane glycoproteins containing an Ig Variable-type (V-type) domain responsible for ligand binding and a cytoplasmic tail which is responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM). Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3ζ, PKCθ and ZAP70 which are involved in the CD3 T-cell signaling cascade [7; 10; 11; 12]. The mechanism by which PD-1 down modulates T-cell responses is similar to, but distinct from that of CTLA-4 as both molecules regulate an overlapping set of signaling proteins [13; 14]. PD-1 was shown to be expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B-cells, T regs and Natural Killer cells [15; 16]. Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells [17]. The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types, including non-hematopoietic tissues as well as in various tumors [18; 19; 20; 13]. Both ligands are type I transmembrane receptors containing both IgV- and IgC-like domains in the extracellular region and contain short cytoplasmic regions with no known signaling motifs. Binding of either PD-1 ligand to PD-1 inhibits T-cell activation triggered through the T-cell receptor. PD-L1 is expressed at low levels on

various non-hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments. PD-L2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T-cell function in peripheral tissues [13]. Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. PD-1 has been suggested to regulate tumor-specific T-cell expansion in patients with melanoma (MEL) [21]. This suggests that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention.

Pembrolizumab (MK-3475) (previously known as SCH 900475) is a potent and highly selective humanized monoclonal antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2.

4.1.2 Pre-clinical and Clinical Trials

Therapeutic studies in mouse models have shown that administration of antibodies blocking PD-1/PD-L1 interaction enhances infiltration of tumor-specific CD8+ T-cells and leads ultimately to tumor rejection, either as a mono-therapy or in combination with other treatment modalities. Anti-mouse PD-1 or anti-mouse PD-L1 antibodies have demonstrated anti-tumor responses as a mono-therapy in models of squamous cell carcinoma, pancreatic carcinoma, MEL and colorectal carcinoma. Blockade of the PD-1 pathway effectively promoted CD8+ T-cell infiltration into the tumor and the presence of IFN-γ, granzyme B and perforin, indicating that the mechanism of action involved local infiltration and activation of effector T-cell function in vivo [22; 23; 24; 25; 26; 27]. Experiments have confirmed the in vivo efficacy of PD-1 blockade as a mono-therapy as well as in combination with chemotherapy in syngeneic mouse tumor models (see the Investigator's Brochure [IB]).

Patients with recurrent and/or metastatic head and neck squamous cell carcinoma who have progressed on platinum and cetuximab have limited treatment options. Treatment options commonly utilized in this setting include palliative chemotherapy such as methotrexate or taxanes. After failure of front-line chemotherapy in the recurrent/metastatic setting, objective responses to subsequent cytotoxic chemotherapy are uncommon. For example, a Phase III trial comparing weekly intravenous methotrexate with gefitinib, an epidermal growth factor receptor tyrosine kinase inhibitor in a heavily pretreated population resulted in an overall response rate to methotrexate of 4 percent in 152 patients, with a median overall survival of 6.7 months [28].

4.1.3 Ongoing Clinical Trials

Ongoing clinical trials of pembrolizumab are being conducted in advanced melanoma, non-small cell lung cancer, a number of advanced solid tumor indications and hematologic malignancies. For study details please refer to the IB.

Trials evaluating pembrolizumab in head and neck cancer have demonstrated clinical activity in patients with recurrent and/or metastatic disease. KEYNOTE 012 is a Phase Ib study of pembrolizumab in patients with human papillomavirus (HPV)-negative and HPV-positive head and neck cancer. This trial enrolled an initial 60 patient cohort with recurrent and/or metastatic squamous cell carcinoma of the head and neck for treatment with single agent pembrolizumab. Preliminary results from this cohort were reported at the Annual Meeting of the American Society of Clinical Oncology (ASCO) in 2014 [29], showing an overall response rate (confirmed and unconfirmed) of 19.6% (10 partial responses [PRs], 1 complete response [CR] out of 56 patients evaluable for response). An additional 16/56 patients (28.6%) experienced stable disease (SD), with 51% of patients experiencing some numerical decrease in tumor burden from baseline. Seventeen total patients with CR, PR, or SD remain on therapy at the time of the reporting for > 6 months. There were no new or unexpected toxicity signals in this patient cohort, with infrequent grade 3-4 drug-related (DR) adverse events (AEs).

Preliminary PD-L1 biomarker data from KEYNOTE 012 suggests that the response rate may be enhanced for patients with high PD-L1 IHC expression. Using a Youden-Index derived PD-L1 IHC cutpoint, the response rate (RR) in patients with high PD-L1 expression was 45.5% (5/11), compared to 11.4% (5/44) in low PD-L1 expression patients.

More recently, when analyzed for durability of response, evolving information show that PD-L1 expression with a 1% cut-off (≥1%) for IHC testing, using a combined positive score (CPS) that accounts for PD-L1 expression in both tumor and infiltrating immune cells may be a better predictor of response to pembrolizumab. When analyzed by PD-L1 1% CPS positive in the KEYNOTE 012, median PFS and OS were longer for those with demonstrable evidence of PD-L1 expression in either tumor or infiltrating immune cells. Importantly, using a cut-off of 1% CPS to define PD-L1 positive tumors, 81.1% of the KEYNOTE 012 metastatic/recurrent HNSCC tumors were PD-L1 positive, with observed objective response rates of 21.5% for patients with PD-L1 positive tumors and 4% for patients with PD-L1 negative tumors. Therefore, based on the evolving information obtained from further analysis of the KEYNOTE 012 study, we plan to evaluate PD-L1 expression using a 1% CPS cut-off in addition to the 50% TPS previously specified. We plan to correlate PD-L1 expression with clinical outcome according to both IHC criteria.

Additional biomarker data on pembrolizumab (MK-3475) in subjects with non-small cell lung cancer (NSCLC) provide evidence that pretreatment tumor PD-L1 expression is a predictor of response. In subjects with evaluable tumor PD-L1 expression, a higher rate of radiologic responses by RECIST v1.1 (and irRC) occurred in subjects with tumors strongly positive for PD-L1, suggesting that PD-L1 may be a predictive biomarker of anti-PD-1 activity. This hypothesis that PD-L1 may predict potential response to anti-PD-1 therapy is consistent with the previously published results of Topalian et al. [30], who examined PD-L1 expression in the archival specimens of 42 of the 296 subjects treated with the PD-1 inhibitor nivolumab. Of those 17 subjects whose tumor cells did not stain positive for PD-L1 using a 5% threshold of tumor cell surface expression, no objective response by RECIST 1.1 was observed. However, among the 25 subjects whose tumor cells were considered positive for PD-L1, 9 responded (36%).

In general, pembrolizumab was well tolerated with 58.3% reporting a DR AE and 16.7% reporting a Grade 3-5 DR AE. DR AEs with an incidence ≥ 5% were fatigue (10, 16.7%), pruritus (6, 10%), rash (5, 8.3%), nausea (4, 6.7%), decreased appetite (3, 5.0%), and myalgia (3, 5.0%). Of these DR AEs, Grade 3-5 was seen in rash (2, 3.3%). The reported pre-specified AEs were adrenal insufficiency (1, 1.7%); diarrhea (1, 1.7%); pruritus (1, 1.7%); rash (2, 3.3%); rash, macular (1, 1.7%); pneumonitis (0); alanine aminotransferase (ALT) increase (2, 3.3%); and aspartate aminotransferase (AST) increase (2, 3.3%) [29].

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

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

This is a multicenter, nonrandomized, single-cohort trial of pembrolizumab (MK-3475) in subjects with recurrent and/or metastatic head and neck squamous cell carcinoma. Trials evaluating pembrolizumab (MK-3475) in head and neck cancer have demonstrated clinical activity in subjects with recurrent and/or metastatic disease. Refer to Section 4.1.3, Ongoing Clinical Trials, for results from the Phase Ib study of pembrolizumab in patients with HPV-negative and HPV-positive head and neck cancer (KEYNOTE 012).

Participation in this trial will be dependent upon supplying a newly obtained core or excisional biopsy of a tumor lesion. The tissue specimens will be evaluated at a central laboratory for expression status of PD-L1 in a retrospective analysis, thus tissue availability, but not high biomarker expression is required for study entry. Therefore subjects will be enrolled onto this trial irrespective of PD-L1 expression (including subjects whose tumors do not express PD-L1). If emerging biomarker data from on-going subjects being treated with pembrolizumab (MK-3475) in KEYNOTE 012 does not confirm the clinical utility of the PD-L1 biomarker in newly obtained tumor tissue to predict response to pembrolizumab (MK-3475), the newly obtained tumor sample may become optional, and may be substituted by an archival tumor tissue sample.

4.2.2 Rationale for Dose Selection/Regimen/Modification

An open-label Phase I trial (KEYNOTE 001) is being conducted to evaluate the safety and clinical activity of single agent pembrolizumab (MK-3475). The dose escalation portion of this trial evaluated three dose levels, 1 mg/kg, 3 mg/kg, and 10 mg/kg, administered every 2 weeks (Q2W) in subjects with advanced solid tumors. All three dose levels were well tolerated and no dose-limiting toxicities were observed. This first in human study of pembrolizumab (MK-3475) showed evidence of target engagement and objective evidence of tumor size reduction at all dose levels (1 mg/kg, 3 mg/kg and 10 mg/kg Q2W). No MTD has been identified.

In KEYNOTE 001, two randomized cohort evaluations of melanoma subjects receiving pembrolizumab (MK-3475) at a dose of 2 mg/kg versus 10 mg/kg Q3W have been completed, and one randomized cohort evaluating of 10 mg/kg Q3W versus 10 mg/kg Q2W has also been completed. The clinical efficacy and safety data demonstrate a lack of clinically important differences in efficacy response or safety profile at these doses. For example, in Cohort B2, advanced melanoma subjects who had received prior ipilimumab therapy were randomized to receive pembrolizumab (MK-3475) at 2 mg/kg versus 10 mg/kg Q3W. The ORR was 26% (21/81) in the 2mg/kg group and 26% (20/76) in the 10 mg/kg group (FAS). The proportion of subjects with drug-related AE, grade 3-5 drug-related AE, serious drug-related AE, death or discontinuation due to an AE was comparable between groups or lower in the 10 mg/kg group. In Cohort B3, advanced melanoma subjects (irrespective of prior ipilimumab therapy) were randomized to receive pembrolizumab (MK-3475) at 10 mg/kg Q2W versus 10 mg/kg Q3W. The ORR was 30.9% (38/123) in the 10mg/kg Q2W group and 24.8% (30/121) in the 10 mg/kg Q3W group (APaT). The proportion of subjects with drug-related AE, grade 3-5 drug-related AE, serious drug-related AE, death or discontinuation due to an AE was comparable between groups.

PK data analysis of pembrolizumab (MK-3475) administered Q2W and Q3W showed slow systemic clearance, limited volume of distribution, and a long half-life (refer to IB). Pharmacodynamic data (IL-2 release assay) suggested that peripheral target engagement is durable (>21 days). This early PK and pharmacodynamic data provides scientific rationale for testing a Q3W dosing schedule. Because Q3W dosing is more convenient for subjects, Q3W dosing will be evaluated in this protocol.

The rationale for further exploration of 2mg/kg and comparable doses of MK-3475 in solid tumors is based on: 1) similar efficacy and safety of MK-3475 when dosed at either 2 mg/kg or 10 mg/kg Q3W in melanoma patients, 2) the flat exposure-response relationships of MK-3475 for both efficacy and safety in the dose ranges of 2 mg/kg Q3W to 10 mg/kg Q3W, 3) the lack of effect of tumor burden or indication on distribution behavior of MK-3475 (as assessed by the population PK model) and 4) the assumption that the dynamics of MK-3475 target engagement will not vary meaningfully with tumor type.

The choice of the 200 mg Q3W as an appropriate dose for the switch to fixed dosing is based on simulations performed using the population PK model of MK-3475 showing that the fixed dose of 200 mg every 3 weeks will provide exposures that 1) are optimally consistent with those obtained with the 2 mg/kg dose every 3 weeks, 2) will maintain individual patient exposures in the exposure range established in melanoma as associated with maximal efficacy response and 3) will maintain individual patients exposure in the exposure range established in melanoma that are well tolerated and safe.

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

The primary efficacy objective of this trial is to evaluate the anti-tumor activity of pembrolizumab (MK-3475) in subjects with recurrent and/or metastatic head and neck squamous cell carcinoma (HNSCC). Response rates per RECIST 1.1 [31] as assessed by the central vendor will be used as the primary response rate efficacy endpoint.

RECIST 1.1 will also be used by the local site for treatment decisions. However RECIST 1.1 will be adapted to account for the unique tumor response profile seen with treatment of pembrolizumab (MK-3475).

Immunotherapeutic agents such as pembrolizumab (MK-3475) may produce antitumor effects by potentiating endogenous cancer-specific immune responses which may be functionally anergic. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents, and can manifest a clinical response after an initial increase in tumor burden or even the appearance of new lesions. Standard RECIST criteria may not provide a complete response assessment of immunotherapeutic agents such as pembrolizumab (MK-3475). Therefore, RECIST 1.1 will be used with the following adaptation, termed Modified RECIST 1.1.

If radiologic imaging shows PD, tumor assessment should be repeated ≥ 4 weeks later in order to confirm PD with the option of continuing treatment per below while awaiting radiologic confirmation of progression. If repeat imaging shows < 20% tumor burden compared to nadir, stable or improved previous new lesion (if identified as cause for initial PD), and stable/improved non-target disease (if identified as cause for initial PD), PD is not confirmed. Treatment may be continued as per treatment calendar.

If repeat imaging confirms progressive disease due to any of the scenarios listed below, subjects will be discontinued from trial treatment (exception noted in Section 7.1.2.6.3). In determining whether or not the tumor burden has increased or decreased, Investigators should consider all target lesions as well as non-target lesions.

Scenarios where PD is confirmed at repeat imaging:

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

In subjects who have initial evidence of radiological PD, it is at the discretion of the treating physician whether to continue a subject on trial treatment until repeat imaging is obtained a

minimum of 4 weeks later. This decision should be based on the clinical judgment of the subject's overall clinical condition, including performance status, clinical symptoms, and laboratory data. Subjects may receive treatment while waiting for confirmation of PD if they are clinically stable as defined by the following criteria:

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

When feasible, subjects should not be discontinued until progression is confirmed. This allowance to continue treatment despite initial radiologic progression takes into account the observation that some subjects can have a transient tumor flare in the first few months after the start of immunotherapy, but with subsequent disease response. Subjects that are deemed clinically unstable are not required to have repeat imaging for confirmation of progressive disease. Supportive retrospective independent review of all imaging time points will be performed for this trial using Modified RECIST 1.1.

4.2.3.2 Safety Endpoints

The primary safety objective of this trial is to characterize the safety and tolerability of pembrolizumab (MK-3475) in subjects with HNSCC. The primary safety analysis will be based on subjects who experienced toxicities as defined by CTCAE criteria. Safety will be assessed by quantifying the toxicities and grades experienced by subjects who have received pembrolizumab (MK-3475), including serious adverse events (SAEs) and events of clinical interest (ECIs).

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

4.2.3.3 Planned Exploratory Biomarker Research

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

Assays may include but are not be limited to:

Immunohistochemistry

In addition to PD-L1 expression, other exploratory biomarkers (e.g. PD-1 expression, markers of T-cell phenotype) may also be evaluated.

Transcriptional Analyses

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

Gene Analyses

The application of new technologies, such as next generation sequencing, has provided scientists the opportunity to define certain tumor types at the genetic level as being 'hypermutated' or can detect the presence of specific T-cell clones within the tumor microenvironment or in the peripheral blood. There is a potential that the hypermutated state and/or increased T-cell clonality may correlate with response to pembrolizumab (MK-3475) therapy, and/or that the converse, 'hypomutated' state or lack of dominant T-cell clones may correlate with non-response.

In addition, understanding genetic determinants of drug response is an important endeavor during medical research. This research will evaluate whether genetic variation within a clinical trial population correlates with response to the treatment(s) under evaluation. If genetic variation is found to predict efficacy or adverse events, the data might inform optimal use of therapies in the patient population.

4.2.3.4 Future Biomedical Research

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

Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol (as part of the main trial) and will only be conducted on specimens from appropriately consented subjects. The objective of collecting specimens for Future Biomedical Research is to explore and identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments. For instance, exploratory pharmacogenetic (PGt) studies may be performed if significant

Pharmacokinetic/Pharmacodynamic (PK/PD) relationships are observed or adverse events are identified. Genomic markers of disease may also be investigated. Such retrospective pharmacogenetic studies will be conducted with appropriate biostatistical design and analysis and compared to PK/PD results or clinical outcomes. Any significant PGt relationships to outcome would require validation in future clinical trials. The overarching goal is to use such information to develop safer, more effective drugs/vaccines, and/or to ensure that subjects receive the correct dose of the correct drug/vaccine at the correct time. The details of this Future Biomedical Research sub-trial are presented in Section 12.2 - Collection and Management of Specimens for Future Biomedical Research. Additional informational material for institutional review boards/ethics committees (IRBs/ERCs) and investigational site staff is provided in Section 12.3.

4.3 Benefit/Risk

Subjects in clinical trials generally cannot expect to receive direct benefit from pembrolizumab (MK-3475) during participation, as clinical trials are designed to provide information about the safety and effectiveness of an investigational medicine.

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

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

Male/Female subjects with head and neck squamous cell carcinoma 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 day of signing informed consent.

3. Have histologically or cytologically-confirmed recurrent or metastatic head and neck squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, and larynx that is considered incurable by local therapies.

    a. Note: Subjects with oropharynx cancer must have an assessment of HPV status from tumor tissue.

4. Be resistant to platinum (either cisplatin or carboplatin) and cetuximab-based therapy. Resistance is defined as tumor progression or recurrence within 6 months of the last dose of platinum and cetuximab therapy in the adjuvant (e.g. with radiation after surgery), primary (e.g. with radiation), recurrent, or metastatic setting. Subject must be resistant to both platinum and cetuximab.

    a. Note: Any number of previous systemic regimens given for recurrent and/or metastatic disease is allowed.

    b. Note: Platinum and cetuximab do not need to be given concurrently (i.e. can be given with sequential regimens) however the patient must have recurred within 6 months of the last dose for each of these therapies.

5. Have provided tissue for PD-L1 biomarker analysis from a newly obtained core or excisional biopsy. Repeat samples may be required if adequate tissue is not provided.

    a. Note: Subjects for whom newly obtained samples cannot be obtained (e.g. inaccessible or subject safety concern) may submit an archived specimen only upon agreement from the Sponsor.

    b. Note: If emerging data does not demonstrate the clinical utility of PD-L1 in newly obtained samples, archived samples may be acceptable.

6. Have measurable disease based on RECIST 1.1 as determined by central review. Tumor lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions.

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

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

Table 1 Adequate Organ Function Laboratory Values

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

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

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

11. Male subjects should agree to use an adequate method of contraception starting with the first dose of study therapy through 120 days after the last dose of study therapy.

5.1.3 Subject Exclusion Criteria

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

1. Has disease that is suitable for local therapy administered with curative intent.

2. Is currently participating in or has participated in a study of an investigational agent or using an investigational device within 4 weeks prior to the first dose of trial treatment.

   Note: Subjects who have entered the follow-up phase of an investigational study may participate as long as it has been 4 weeks since the last dose of the previous investigational agent or device.

3. 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.

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 adverse events due to agents 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 adverse events due to a previously administered agent.

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

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

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

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

8. Has an active autoimmune disease that has required systemic treatment in past 2 years (i.e., with use of disease modifying agents, corticosteroids, or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.

9. Has active, non-infectious 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 received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent or if the patient has previously participated in Merck MK-3475 clinical trials.

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

16. Has known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected).

17. Has received a live vaccine within 30 days of planned start of study therapy.

    Note: Seasonal influenza vaccines for injection are generally inactivated flu vaccines and are allowed; however intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines, and are not allowed.

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

5.2 Trial Treatment(s)

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

Table 2 Trial Treatment

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period	Use
Pembrolizumab (MK-3475)	200 mg	Q3W	IV infusion	Day 1 of each 3 week cycle	Experimental

Trial treatment should begin on or as close as possible to the date of treatment allocation/assignment.

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 dose of pembrolizumab (MK-3475) to be used in this trial is provided in Section 4.0 – Background & Rationale. Details on preparation and administration of pembrolizumab (MK-3475) are provided in the Pharmacy Manual.

5.2.1.2 Dose Modification (Escalation/Titration/Other)

Adverse events (both non-serious and serious) associated with pembrolizumab exposure may represent an immunologic etiology. These adverse events may occur shortly after the first dose or several months after the last dose of treatment. Pembrolizumab must be withheld for drug-related toxicities and severe or life-threatening AEs as per Table 3 below. See Section 5.6 and the Events of Clinical Interest Guidance Document for supportive care guidelines, including use of corticosteroids.

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

General instructions:

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

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

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

Immune-related AEs	Toxicity grade or conditions (CTCAEv4.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
Myocarditis	Grade 1 or 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
All other immune-related AEs	Intolerable/ persistent Grade 2	Withhold	• Based on type and severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3	Withhold or discontinue based on the type of event. Events that require discontinuation include and not limited to: Guillain-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 withhold of pembrolizumab is required, pembrolizumab may be resumed when AE resolves to ≤ Grade 2 and is controlled with hormonal replacement therapy or achieved metabolic control (in case of T1DM).				

In case toxicity does not resolve to Grade 0-1 within 12 weeks after last infusion, trial treatment should be discontinued after consultation with the Sponsor. Subjects who experience a recurrence of the same severe or life-threatening event at the same grade or greater with rechallenge of pembrolizumab (MK-3475) should be discontinued from trial treatment. With Investigator and Sponsor agreement, subjects with a laboratory adverse event still at Grade 2 after 12 weeks may continue treatment in the trial only if asymptomatic and controlled. For information on the management of adverse events, see Section 5.6.1.

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

5.2.2 Timing of Dose Administration

Pembrolizumab (MK-3475) should be administered on Day 1 of each three week cycle after all procedures/assessments have been completed as detailed on the Trial Flow Chart (Section 6.0). Trial treatment may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons.

All trial treatments will be administered on an outpatient basis.

5.2.2.1 Pembrolizumab (MK-3475)

Pembrolizumab (MK-3475) 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). The reason for any delay in infusion outside of the protocol specified window should be documented in the patient’s chart and recorded in the case report form (CRFs). Central venous catheters (CVCs) or vascular access devices (VADs) may be used to administer treatment.

The Pharmacy Manual contains specific instructions for the preparation of the pembrolizumab (MK-3475) infusion fluid and administration of infusion solution.

Treatment after initial evidence of radiologic disease progression

Immunotherapeutic agents such as pembrolizumab (MK-3475) may produce antitumor effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents, and can manifest as a clinical response after an initial increase in tumor burden or even the appearance of new lesions.

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

burden compared to the initial scan demonstrating PD, treatment may be continued as per treatment calendar. If repeat imaging confirms progressive disease, subjects will be discontinued from study therapy (exception noted in Section 7.1.2.6.3). In determining whether or not the tumor burden has increased or decreased, Investigators should consider all target lesions as well as non-target lesions.

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

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

Table 4 Imaging and Treatment after 1st Radiologic Evidence of PD

	Clinically Stable		Clinically Unstable	
	Imaging	Treatment	Imaging	Treatment
1st radiologic evidence of PD	Repeat imaging at ≥ 4 weeks to confirm PD	May continue study treatment at the Investigator's discretion while awaiting confirmatory scan	Repeat imaging at ≥ 4 weeks to confirm PD if possible	Discontinue treatment
Repeat scan confirms PD	No additional imaging required	Discontinue treatment (exception noted in Section 7.1.2.6.3)	No additional imaging required	N/A
Repeat scan shows SD, PR or CR	Continue regularly scheduled imaging assessments	Continue study treatment at the Investigator's discretion	Continue regularly scheduled imaging assessments	May restart study treatment if condition has improved and/or clinically stable per Investigator's discretion

5.2.3 Trial Blinding/Masking

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

Although this is an open-label trial, the study team at the Sponsor consisting of the clinical, statistics and data management personnel will remain blinded to PD-L1 patient-level biomarker results until the time that a study report is written. While the study team is blinded to PD-L1 patient-level biomarker results, access to the PD-L1 patient-level biomarker results will be limited to an unblinded Sponsor statistician and Sponsor statistical programmer who will be responsible for data review but who have no other responsibilities associated with the trial.

5.3 Randomization or Treatment Allocation

Allocation will occur centrally using an interactive voice response system / integrated web response system (IVRS/IWRS). There is one treatment arm. Subjects will be assigned pembrolizumab (MK-3475).

5.4 Stratification

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

5.5 Concomitant Medications/Vaccinations (Allowed & Prohibited)

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

5.5.1 Acceptable Concomitant Medications

All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the 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 may also be included on the CRF.

All concomitant medications received within 30 days before the screening visit and 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered after 30 days after the last dose of trial treatment should be recorded for SAEs and ECIs as defined in Section 7.2.

5.5.2 Prohibited Concomitant Medications

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

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy
- Investigational agents other than pembrolizumab (MK-3475)
- Radiation therapy
  - Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed after consultation with Sponsor.
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, intranasal influenza, rabies, BCG, and typhoid vaccine.
- Glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.

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

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

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

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

5.6 Rescue Medications & Supportive Care

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

Note: if after the evaluation the event is determined not to be related, the investigator is instructed to follow the ECI reporting guidance but does not need to follow the treatment guidance (as outlined in the ECI guidance document). Refer to Section 5.2.1 for dose modification.

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event. Suggested conditional procedures, as appropriate, can be found in the ECI guidance document.

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

  Subjects should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus).
    - All subjects who experience diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion. For Grade 2 or higher diarrhea, consider GI consultation and endoscopy to confirm or rule out colitis.
    - For **Grade 2 diarrhea/colitis** that persists greater than 3 days, administer oral corticosteroids.
    - For **Grade 3 or 4 diarrhea/colitis** that persists > 1 week, treat with intravenous steroids followed by high dose oral steroids.
    - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
- **Type 1 diabetes mellitus (if new onset, including diabetic ketoacidosis [DKA]) or ≥ Grade 3 Hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA)**
    - For **T1DM** or **Grade 3-4** Hyperglycemia
        - Insulin replacement therapy is recommended for Type I diabetes mellitus and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria.
        - Evaluate patients with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.

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

  Thyroid disorders can occur at any time during treatment. Monitor patients for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders.
    - **Grade 2** hyperthyroidism events (and **Grade 2-4** hypothyroidism):
        - In hyperthyroidism, non-selective beta-blockers (e.g. propranolol) are suggested as initial therapy.
        - In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyronine, is indicated per standard of care.
    - **Grade 3-4** hyperthyroidism
        - Treat with an initial dose of IV corticosteroid followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
- **Hepatic**:
    - For **Grade 2** events, monitor liver function tests more frequently until returned to baseline values (consider weekly).
        - Treat with IV or oral corticosteroids
    - For **Grade 3-4** events, treat with intravenous corticosteroids for 24 to 48 hours.
    - When symptoms improve to Grade 1 or less, a steroid taper should be started and continued over no less than 4 weeks.
- **Renal Failure or Nephritis**:
    - For **Grade 2** events, treat with corticosteroids.
    - For **Grade 3-4** events, treat with systemic corticosteroids.
    - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

- **Management of Infusion Reactions**: Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion.

Table 5 below shows treatment guidelines for subjects who experience an infusion reaction associated with administration of pembrolizumab (MK-3475).

Table 5 Infusion Reaction Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 hrs	**Stop Infusion and monitor symptoms.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. **Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.**	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab (MK-3475) with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **Subject is permanently discontinued from further trial treatment administration.**	No subsequent dosing
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.		

5.7 Diet/Activity/Other Considerations

5.7.1 Diet

Subjects should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea or vomiting. Percutaneous endoscopic gastrostomy (PEG) tubes are acceptable for prophylactic feeding.

5.7.2 Contraception

Pembrolizumab (MK-3475) may have adverse effects on a fetus in utero. Furthermore, it is not known if pembrolizumab (MK-3475) has transient adverse effects on the composition of sperm. Non-pregnant, non-breast-feeding women may be enrolled if they are willing to use 2 methods of birth control or are considered highly unlikely to conceive. Highly unlikely to conceive is defined as 1) surgically sterilized, or 2) postmenopausal (a woman who is ≥45 years of age and has not had menses for greater than 1 year will be considered postmenopausal), or 3) not heterosexually active for the duration of the study. The two birth control methods can either be two barrier methods or a barrier method plus a hormonal method to prevent pregnancy. Subjects should start using birth control from study Visit 1 throughout the study period up to 120 days after the last dose of study therapy.

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

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

5.7.3 Use in Pregnancy

If a subject inadvertently becomes pregnant while on treatment with pembrolizumab (MK-3475), the subject will immediately be removed from the study. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the Sponsor without delay and within 24 hours if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor. If a male subject impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to the Sponsor and followed as described above and in Section 7.2.2.

5.7.4 Use in Nursing Women

It is unknown whether pembrolizumab (MK-3475) is excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, subjects who are breast-feeding are not eligible for enrollment.

5.8 Subject Withdrawal/Discontinuation Criteria

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

In this trial, a subject may discontinue from treatment but continue to participate in the regularly scheduled activities, as long as the subject does not withdraw consent. Once a subject has discontinued treatment, even though he/she continues to be monitored in the trial, he/she may be allowed to begin treatment again if deemed medically appropriate.

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

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

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

- The subject or legal representative (such as a parent or legal guardian) withdraws consent for treatment
- Confirmed radiographic disease progression

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

  Note: A subject may be granted an exception to continue on treatment with confirmed radiographic progression if clinically stable or clinically improved, please see Section 7.1.2.6.3.
- Unacceptable adverse experiences as described in Section 5.2.1.2
- Intercurrent illness that prevents further administration of treatment
- Investigator's decision to withdraw the subject
- The subject has a confirmed positive serum pregnancy test

- Noncompliance with trial treatment or procedure requirements
- The subject is lost to follow-up
- Completed 24 months of treatment with pembrolizumab (MK-3475)

  Note: 24 months of study medication is calculated from the date of first dose. Subjects who stop pembrolizumab (MK-3475) after 24 months may be eligible for up to one year of additional study treatment if they progress after stopping study treatment provided they meet the requirements detailed in Section 7.1.5.2.1.

- Administrative reasons

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

5.8.1 Discontinuation of Study Therapy after CR

Discontinuation of treatment may be considered for subjects who have attained a confirmed CR that have been treated for at least 24 weeks with pembrolizumab (MK-3475) and had at least two treatments with pembrolizumab (MK-3475) beyond the date when the initial CR was declared. Subjects who then experience radiographic disease progression may be eligible for up to one year of additional treatment with pembrolizumab (MK-3475) at the discretion of the investigator if no cancer treatment was administered since the last dose of pembrolizumab (MK-3475), the subject meets the safety parameters listed in the Inclusion/Exclusion criteria, and the trial is open. Subjects will resume therapy at the same dose and schedule at the time of initial discontinuation. Additional details are provided in Section 7.1.5.2.1.

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 completes the last study related phone call or visit, discontinues from the trial or is lost to follow-up (i.e. the subject is unable to be contacted by the investigator). Upon study completion, subjects are discontinued and enrolled in a pembrolizumab extension trial.

5.11 Clinical Criteria for Early Trial Termination

There are no pre-specified criteria for terminating the trial early.

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

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

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

2. Poor adherence to protocol and regulatory requirements

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

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

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

6.0 TRIAL FLOW CHART

6.1 Initial Treatment Phase and Second Course Phase (Retreatment)

6.1.1 Initial Treatment Phase

Trial Period:	Screening Phase		Treatment Cycles[a]						End of Treatment	Post-Treatment		
Treatment Cycle/Title:	Screening (Visit 1)		1	2	3	4	To be repeated beyond 6 cycles: 5	6	Discon	Safety Follow-up	Follow Up Visits[b]	Survival Follow-up[c]
Scheduling Window (Days)[d]:	-42 to -1	-28 to -1	+3[d]	± 3	± 3	± 3	± 3	± 3	At time of discon	30 days post discon	Every 6 weeks post discon	Approx. every 12 weeks
Administrative Procedures												
Informed Consent	X[e]											
Informed Consent for Future Biomedical Research		X[f]										
Inclusion/Exclusion Criteria		X										
Subject Identification Card		X										
Demographics and Medical History		X										
Prior and Concomitant Medication Review[g]		X	X	X	X	X	X	X	X	X		
Trial Treatment Administration[h]			X	X	X	X	X	X				
Post-study Anticancer Therapy Status											X	X
Survival Status[c]			<------	------	------	------	------	------	------	------	------>	X
Clinical Procedures/Assessments												
Review Adverse Events		X	X	X	X	X	X	X	X	X[i]	X[i]	
12-Lead ECG (Local)[x]		X										
Full Physical Examination[x]		X							X			
Directed Physical Examination			X	X	X	X	X	X				
Vital Signs and Weight[k]		X	X	X	X	X	X	X	X	X	X	
ECOG Performance Status		X	X	X	X	X	X	X	X	X	X	
Laboratory Procedures/Assessments: analysis performed by LOCAL laboratory												
Pregnancy Test – Serum or Urine[l]		X										
PT/INR and aPTT[m]		X[n]										
CBC with Differential[o]		X[n]		X	X	X	X	X	X	X[p]		
Chemistry Panel[o]		X[n]		X	X	X	X	X	X	X[p]		

Trial Period:	Screening Phase		Treatment Cycles[a]						End of Treatment	Post-Treatment		
Treatment Cycle/Title:	Screening (Visit 1)		1	2	3	4	To be repeated beyond 6 cycles: 5	To be repeated beyond 6 cycles: 6	Discon	Safety Follow-up	Follow Up Visits[b]	Survival Follow-up[c]
Scheduling Window (Days)[d]:	-42 to -1	-28 to -1	+3[d]	± 3	± 3	± 3	± 3	± 3	At time of discon	30 days post discon	Every 6 weeks post discon	Approx. every 12 weeks
Urinalysis[o]		X[n]		X		X		X[j]		X[p]		
T3, FT4 and TSH[o]		X[n]		X		X		X[j]		X[p]		
HPV Status[w]	X											
Laboratory Procedures/Assessments: analysis performed by CENTRAL laboratory												
Pharmacokinetics[q]			X[q]	X[q]		X[q]						
Anti-MK-3475 Antibodies[q]			X[q]	X[q]		X[q]						
Correlative Blood Samples[r]			X	X	X				X			
Blood for Genetics[v]			X									
Efficacy Measurements												
Tumor Imaging		X[s]				X[t]		X[t]			X[b]	
Tumor Tissue Collection												
Newly Obtained Tissue Collection	X[u]											

a. In general, assessments/procedures are to be performed on Day 1 and prior to the first dose of treatment for each cycle unless otherwise specified. Treatment cycles are 3 weeks. Imaging should be performed at 9 weeks after 1st dose and every 6 weeks thereafter (42 days ± 7 days) regardless of any treatment delays. After 1 year, imaging will occur every 9 weeks (± 7 days).

b. In subjects who discontinue study therapy without documented disease progression, every effort should be made to continue monitoring their disease status every 6 weeks (± 7 days) in the first year and every 9 weeks (± 7 days) after year 1 until (1) the start of new anti-cancer treatment, (2) disease progression, (3) death, or (4) notified by the Sponsor, whichever occurs first. If imaging assessment beyond the protocol-required imaging time frame is necessary, the reason for the extended imaging schedule should be documented in the subject's chart and recorded in the Oncologic Response-Solid Tumor (ORST) eCRF for each imaging assessment completed within the extended time frame. The maximum imaging time frame allowed is no greater than twice the imaging time frame noted for the specific year of follow-up (ie, first year follow-up is every 6 weeks; the maximum imaging schedule allowance is every 12 weeks. Second year follow-up is every 9 weeks; the maximum imaging schedule allowance is every 18 weeks). Every effort should be made to target the protocol-required imaging schedule as closely as possible; however, in the interest of the subject's continued participation in the follow-up phase of the study, the extended imaging time frame may be considered at the discretion of the investigator.

c. After the start of new anti-cancer treatment or documented local site-assessed disease progression, the subject should be contacted by telephone approximately every 12 weeks to assess for survival status. Updated survival status may be requested by the Sponsor at any time during the course of the trial. Upon Sponsor notification, all subjects who do not/will not have a scheduled trial visit or trial contact during the Sponsor-defined time period will be contacted for their survival status (excluding subjects who have a death event previously recorded).

d. In general, the window for each visit is ± 3 days unless otherwise noted. Cycle 1 treatment must be given within 3-5 days of enrollment.

e. Written consent must be obtained prior to performing any protocol specified procedure. Please note that the window for acquiring the "newly obtained" tissue specimen is within 42 days of the first dose of study drug and written consent should be obtained prior to acquiring the specimen if a biopsy for the study is performed. 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 window specified for screening procedures (e.g., within 28 days

Trial Period:	Screening Phase		Treatment Cycles[a]						End of Treatment	Post-Treatment		
Treatment Cycle/Title:	Screening (Visit 1)		1	2	3	4	To be repeated beyond 6 cycles: 5	To be repeated beyond 6 cycles: 6	Discon	Safety Follow-up	Follow Up Visits[b]	Survival Follow-up[c]
Scheduling Window (Days)[d]:	-42 to -1	-28 to -1	+3[d]	± 3	± 3	± 3	± 3	± 3	At time of discon	30 days post discon	Every 6 weeks post discon	Approx. every 12 weeks

prior to the first dose of trial treatment for required lab tests). Screening number will be assigned when the study informed consent is signed.

f. Signing the informed consent for future biomedical research (FBR) sample is optional. Detailed instructions for the collection and management of specimens for FBR are provided in the appendices of the Central Lab Manual and Section 12.2 of the Protocol.

g. Prior medications – Record all medications taken within 30 days of the screening visit. Concomitant medications – Enter new medications started during the trial through the Safety Follow-up visit. Record all medications taken for SAEs as defined in Section 7.2.

h. Trial treatment may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min). The reason for any delay in infusion outside of the protocol specified window should be documented in the patient's chart and recorded on the eCRFs.

i. Record all AEs occurring within 30 days after the last dose of trial treatment. Report all SAEs (related and unrelated to trial treatment) and ECIs occurring up until 90 days after the last dose of trial treatment or the start of new anti-cancer treatment, whichever comes first. Afterwards, report only SAEs and ECIs that are related to trial treatment.

j. To be repeated every 2 cycles after Cycle 6 up to 1 year.

k. Vital signs to include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at visit 1 only.

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

m. Coagulation factors (PT/INR and aPTT) should be tested as part of the screening procedures for all subjects. Any subject receiving anticoagulant therapy should have coagulation factors monitored closely throughout the trial.

n. Laboratory tests for screening are to be performed within 10 days prior to the first dose of trial treatment. See Section 7.1.3 for details regarding laboratory tests.

o. After Cycle 1, lab samples can be collected up to 72 hours prior to the scheduled time point. See Section 7.1.3 for details regarding laboratory tests.

p. Unresolved abnormal labs that are drug related AEs should be followed until resolution. Labs do not need to be repeated after the end of treatment if labs are within normal range.

q. Pre-dose trough PK and anti-pembrolizumab (MK-3475) antibody samples will be collected at Cycles 1, 2, 4, 8, and every 4 cycles thereafter. All pre-dose trough samples should be drawn within 24 hours before infusion of pembrolizumab (MK-3475). Additional post-dose peak PK samples will be drawn within 30 minutes after end of pembrolizumab (MK-3475) infusion at Cycles 1 and 8. An **additional, single PK** sample should be drawn between 72 and 168 hours after Cycle 1 dosing.

r. Blood for correlative studies should be collected prior to Cycle 1, Cycle 2, Cycle 3 and again at treatment discontinuation.

s. The initial tumor imaging will be performed within 28 days prior to the first dose of trial treatment and must be sent to the central vendor to confirm measureable disease for study eligibility. Imaging should include the head, neck, chest, and abdomen; imaging of the pelvis is optional (refer to Section 7.1.2.6). Scans performed as part of routine clinical management are acceptable for use as the screening scan if they are of diagnostic quality, meet the requirements specified by the protocol, and are performed within 28 days prior to the first dose of trial treatment.

t. The first on-study imaging time point will be performed at 9 weeks (± 7 days) after first dose of study treatment and then every 6 weeks (± 7 days) thereafter or more frequently if clinically indicated. After 1 year, imaging time point will occur every 9 weeks (± 7 days). Imaging timing should follow calendar days and should not be adjusted for delays in cycle starts or extension of pembrolizumab (MK-3475) cycle frequencies. Imaging should include the head, neck, chest, and abdomen; imaging of the pelvis is optional (refer to Section 7.1.2.6). The same imaging technique should be used in a subject throughout the trial. On-study scans, including the baseline scans, should be submitted immediately to the central imaging vendor.

u. Baseline tumor tissue for biomarker analysis from a newly obtained core or excisional biopsy (FNA not adequate) must be provided to the central vendor for PD-L1 biomarker testing. Confirmation of tissue adequacy should be received from the central vendor prior to the first dose of trial treatment. A "newly obtained" sample may be obtained up to 42 days prior to

Trial Period:	Screening Phase		Treatment Cycles[a]						End of Treatment	Post-Treatment		
Treatment Cycle/Title:	Screening (Visit 1)		1	2	3	4	To be repeated beyond 6 cycles: 5	To be repeated beyond 6 cycles: 6	Discon	Safety Follow-up	Follow Up Visits[b]	Survival Follow-up[c]
Scheduling Window (Days)[d]:	-42 to -1	-28 to -1	+3[d]	± 3	± 3	± 3	± 3	± 3	At time of discon	30 days post discon	Every 6 weeks post discon	Approx. every 12 weeks

treatment initiation. Tissue beyond the 42-day window may be considered with Sponsor approval as long as no intervening systemic therapy has been administered. Tissue that has been previously irradiated is acceptable. Detailed instructions for tissue collection, process and shipment are provided in the appendices of the Central Lab Manual. If the subject signs the Future Biomedical Research (FBR) consent, any leftover tissue that would ordinarily be discarded at the end of the main study will be retained for FBR.

v. This sample should be drawn for planned, exploratory genetic analysis of DNA unless there is either a documented law or regulation prohibiting collection, or unless the IRB/IEC does not approve of the collection. If the sample is collected, any leftover extracted DNA will be stored for future biomedical research if the subject signs the optional Future Biomedical Research consent.

w. Subjects with oropharynx cancer must have an assessment of HPV status from tumor tissue. Any prior HPV status included in the patient's medical history may be used.

x. In the event that a screening assessment is delayed due to a central vendor assessment (i.e. assessment of measureable disease by the central imaging vendor or assessment of tumor adequacy), Sponsor approval may be granted to allow testing outside of the visit window.

6.1.2 Second Course Phase (Retreatment) for Pembrolizumab (MK-3475)

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

Trial Period:	Treatment Cycles (3-Week Cycles)[a]						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[b]	Survival Follow-up[c]
Scheduling Window (Days)[d]:	+3[d]	± 3	± 3	± 3	± 3	± 3	At time of discon	30 days post discon	Every 6 weeks post discon or per footnote	Approx. every 12 weeks

a. In general, assessments/procedures are to be performed on Day 1 and prior to the first dose of treatment for each cycle unless otherwise specified. Treatment cycles are 3 weeks. Imaging should always be performed every 6 weeks (42 days ± 7 days) regardless of any treatment delays.
b. In subjects who discontinue study therapy without documented disease progression, every effort should be made to continue monitoring their disease status every 6 weeks by radiologic imaging until (1) the start of new anti-cancer treatment, (2) disease progression, (3) death, or (4) until notified by the Sponsor, whichever occurs first. If imaging assessment beyond the protocol-required imaging time frame is necessary, the reason for the extended imaging schedule should be documented in the subject's chart and recorded in the ORST eCRF for each imaging assessment completed within the extended time frame. The maximum imaging time frame allowed is no greater than twice the imaging time frame noted for the specific year of follow up (ie, first year follow-up is every 6 weeks; the maximum imaging schedule allowance is every 12 weeks. Second year follow-up is every 9 weeks; the maximum imaging schedule allowance is every 18 weeks). Every effort should be made to target the protocol-required imaging schedule as closely as possible; however, in the interest of the subject's continued participation in the follow-up phase of the study, the extended imaging time frame may be considered at the discretion of the investigator.
c. After the start of new anti-cancer treatment or disease progression documented by the central imaging vendor, the subject should be contacted by telephone approximately every 12 weeks to assess for survival status. Updated survival status may be requested by the Sponsor at any time during the course of the trial. Upon Sponsor notification, all subjects who do not/will not have a scheduled trial visit or trial contact during the Sponsor-defined time period will be contacted for their survival status (excluding subjects who have a death event previously recorded).
d. In general, the window for each visit is ± 3 days unless otherwise noted.
e. Subjects who either a) attain a CR and discontinue treatment or b) discontinue treatment after 24 months on pembrolizumab for reasons other than disease progression or intolerability may restart trial treatment if they meet the criteria specified in Section 7.1.5.2.1.
f. Concomitant medications – Enter new medications started during the trial through the Safety Follow-up visit. Record all medications taken for AEs as defined in Section 7.2.
g. Subjects who restart treatment should resume at the same dose and cycle interval which they were receiving prior to discontinuation.
h. AEs and laboratory safety measurements will be graded per NCI CTCAE version 4.0. All AEs, whether gradable by CTCAE or not, will also be evaluated for seriousness.
i. Record all AEs occurring within 30 days after the last dose of trial treatment. Report all SAEs (related and unrelated to trial treatment) and ECIs occurring up until 90 days after the last dose of trial treatment or 30 days after the start of new anti-cancer treatment, whichever comes first. Afterwards, report only SAEs and ECIs that are related to trial treatment.
j. To be repeated every 2 cycles after Cycle 5.
k. Vital signs to include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at visit 1 only.
l. For women of reproductive potential, a serum pregnancy test should be performed within 72 hours prior to first dose of retreatment. A urine test can be considered if serum is not appropriate. Pregnancy tests (serum and/or urine tests) should be repeated if required by local guidelines.
m. Coagulation factors (PT/INR and aPTT) should be monitored closely throughout the trial for any subject receiving anticoagulant therapy.
n. Laboratory tests for determining eligibility for retreatment are to be performed within 10 days prior to the first retreatment dose of pembrolizumab. See Section 7.1.3 for details regarding laboratory tests.
o. After Cycle 1, lab samples can be collected up to 72 hours prior to the scheduled time point. See Section 7.1.3 for details regarding laboratory tests. T3 or FT3 can be assayed based on local standards.

Trial Period:	Treatment Cycles (3-Week Cycles)[a]						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[b]	Survival Follow-up[c]
Scheduling Window (Days)[d]:	+3[d]	± 3	± 3	± 3	± 3	± 3	At time of discon	30 days post discon	Every 6 weeks post discon or per footnote	Approx. every 12 weeks

p. Pre-dose trough PK and anti-pembrolizumab antibody samples will be collected at Cycles 1, 2, 4, every 4 cycles thereafter. All pre-dose trough samples should be drawn within 24 hours before infusion of pembrolizumab.
q. A scan must be performed within 28 days prior to restarting treatment with pembrolizumab. Imaging should continue to be performed every 6 weeks (42 ± 7 days) from the first dose of trial treatment or more frequently if clinically indicated. Imaging should include the head, neck, chest, and abdomen; imaging of the pelvis is optional (refer to Section 7.1.2.6). The same imaging technique should be used in a subject throughout the trial. Local reading (investigator assessment with site radiology reading) will be used to determine eligibility and for subject management. The Sponsor will collect radiological assessments for analysis by a central imaging vendor. The processes for image collection and transmission to the central vendor are in the Site Imaging Manual.
r. In subjects who discontinue study therapy, a radiologic evaluation should be performed at the time of treatment discontinuation (i.e., date of discontinue ± 4 week window). If a previous scan was obtained within 4 weeks prior to the date of discontinuation, then a scan at treatment discontinuation does not need to be performed.
s. Unresolved labs that are drug related AEs should be followed until resolution. Labs do not need to be repeated after the end of trial treatment if labs are within normal range.

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 patient qualifies for the trial.

7.1.1.3 Subject Identification Card

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

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

7.1.1.4 Medical History

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

7.1.1.4.1 Disease Details

The investigator or qualified designee will obtain prior and current details regarding the subject's head and neck cancer.

7.1.1.5 Prior and Concomitant Medications Review

7.1.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the subject within 30 days before the screening visit. Prior treatment for head and neck cancer will be recorded separately and not listed as a prior medication.

7.1.1.5.1.1 Prior Treatment Details for Head and Neck Cancer

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

7.1.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the subject during the trial. All medications related to reportable SAEs and ECIs should be recorded as defined in Section 7.2.

7.1.1.5.2.1 Subsequent Anti-Cancer Therapy Status

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

7.1.1.6 Assignment of Screening Number

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

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

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

7.1.1.7 Assignment of Randomization Number

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

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

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

Interruptions from the protocol specified treatment plan for greater than 12 weeks between pembrolizumab (MK-3475) doses require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on subject management.

Administration of trial medication will be witnessed by the investigator and/or trial staff. The total volume of pembrolizumab (MK-3475) infused will be compared to the total volume prepared to determine compliance to each dose of pembrolizumab (MK-3475) administered.

The instructions for preparing and administering pembrolizumab (MK-3475) will be provided in the Pharmacy Manual.

7.1.2 Clinical Procedures/Assessments

7.1.2.1 Adverse Event (AE) Monitoring

The investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs as specified in the Trial Flow Chart and more frequently if clinically indicated. Adverse events will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 4.0 (see Appendix 12.7). Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

For subjects receiving treatment with pembrolizumab (MK-3475) all AEs of unknown etiology associated with pembrolizumab (MK-3475) exposure should be evaluated to determine if it is possibly an event of clinical interest (ECI) of a potentially immunologic etiology (termed immune-related adverse events, or irAEs); see Section 5.6.1.1 and the separate ECI guidance document in the administrative binder regarding the identification, evaluation and management of potential irAEs.

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

7.1.2.2 Physical Exam

7.1.2.2.1 Full Physical Exam

The investigator or clinical designee will perform a complete physical exam during the screening period. Clinically significant abnormal findings should be recorded as medical history. A full physical exam should be performed as specified in the Trial Flow Chart. After the first dose of trial treatment new clinically significant abnormal findings should be recorded as AEs.

7.1.2.2.2 Directed Physical Exam

For cycles that do not require a full physical exam per the Trial Flow Chart, the investigator or qualified designee will perform a directed physical exam as clinically indicated prior to dosing on Day 1 of each treatment cycle. New clinically significant abnormal findings should be recorded as AEs.

7.1.2.3 Vital Signs

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

7.1.2.4 12-Lead Electrocardiogram (ECG)

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

7.1.2.5 Eastern Cooperative Oncology Group (ECOG) Performance Status

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

7.1.2.6 Tumor Imaging and Assessment of Disease

The process for image collection and transmission to the central vendor can be found in the imaging section of the Site Imaging Manual. Tumor imaging may be performed by computed tomography (CT) (preferred) or magnetic resonance imaging (MRI), but the same imaging technique should be used in a subject throughout the trial. CT scan is the more commonly used modality and is preferred for the majority of patients. An MRI can be used if clinically appropriate.

Imaging should include the head, neck, chest, and abdomen at all timepoints specified in the Study Flow Chart. Imaging of the pelvis is optional. A CT from the vertex (of the head) to the thoracic inlet is strongly preferred. If a CT from the vertex is not feasible, then a brain CT may be completed instead. For an individual subject, imaging should be consistent at all timepoints, (i.e. follow-up scans should image the same areas as the baseline area, using the same imaging modality).

Real-time determination of measurable disease by independent radiology review at screening will be used to determine subject eligibility. All tumor imaging including scheduled imaging specified in the Study Flow Chart and unscheduled imaging should be submitted to the central imaging vendor. The Sponsor will also receive radiologic images for a retrospective analysis of subject eligibility and treatment response to be performed by the central vendor, using RECIST 1.1.

7.1.2.6.1 Initial Tumor Imaging

Initial tumor imaging must be performed within 28 days prior to the first dose of trial treatment. The central imaging vendor must review the baseline scan to determine subject eligibility. The baseline imaging scan should be submitted to the central imaging vendor immediately.

Scans performed as part of routine clinical management are acceptable for use as the screening scan if they are of diagnostic quality, meet the requirements specified in the imaging manual, and performed within 28 days prior to the first dose of trial treatment.

7.1.2.6.2 Tumor Imaging During Trial

The first imaging assessment should be performed at 9 weeks (63 days ± 7 days) from the date of 1st dose. Subsequent imaging should be performed every 6 weeks (42 days ± 7 days), more frequently if clinically indicated. Subjects who remain on treatment for a year will have imaging performed every 9 weeks. Imaging should not be delayed for delays in cycle starts.

Per RECIST 1.1, response should be confirmed by a repeat radiographic assessment not less than 4 weeks from the date the response was first documented. The scan for confirmation of response may be performed at the earliest 4 weeks after the first indication of response, or at the next scheduled scan (6 weeks later), whichever is clinically indicated. Imaging should then return to the original schedule beginning with the next protocol-specified timepoint. Subjects who obtain a confirmation scan at 4 weeks do not need to undergo the next scheduled imaging assessment if it is due < 4 weeks later; imaging may resume at the subsequent scheduled timepoint. (e.g. If a subject obtains a scan at Week 13 to confirm a Week 9 response, they will not be required to complete the scheduled Week 15 scan. The next imaging would then occur at Week 21 as usual.)

Imaging should continue to be performed until radiographic disease progression, 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 scan indicating progressive disease in clinically stable subjects. Subjects who have unconfirmed disease progression may continue on treatment until progression is confirmed provided they have met the conditions detailed in Section 7.1.2.6.3.

7.1.2.6.3 Assessment of Disease

RECIST 1.1 will be applied by the central imaging vendor as the primary measure for assessment of tumor response. Scans should be submitted to the central imaging vendor in a timely fashion. Sites should also assess tumor response and progression per modified RECIST 1.1 and this data will be collected in the clinical database. Site assessment of tumor response and progression will be used for all patient decision making in the trial.

Modified RECIST 1.1 is RECIST 1.1 adapted as follows to account for the unique tumor response seen in this class of therapeutics (refer to Section 4.2.2.1).

If radiologic imaging shows PD, tumor assessment may be repeated ≥ 4 weeks later at the site in order to confirm PD with the option of continuing treatment for clinically stable subjects as discussed below in Table 6. Clinically stable is defined by the following criteria:

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

Table 6 Imaging and Treatment after 1st radiologic evidence of PD

	Clinically Stable		Clinically Unstable	
	Imaging	Treatment	Imaging	Treatment
1st radiologic evidence of PD	Repeat imaging at ≥ 4 weeks at site to confirm PD	May continue study treatment at the Investigator's discretion while awaiting confirmatory scan by site	Repeat imaging at ≥ 4 weeks to confirm PD per physician discretion only	Discontinue treatment
Repeat scan confirms PD	No additional imaging required	Discontinue treatment	No additional imaging required	N/A
Repeat scan shows SD, PR or CR	Continue regularly scheduled imaging assessments	Continue study treatment at the Investigator's discretion	Continue regularly scheduled imaging assessments	May restart study treatment if condition has improved and/or clinically stable per Investigator's discretion

In determining whether or not the tumor burden has increased or decreased, investigators should consider all target lesions as well as non-target lesions. Subjects that are deemed clinically unstable are not required to have repeat imaging for confirmation. If radiologic progression is confirmed (by subsequent scan) then the subject will be discontinued from trial treatment.

If radiologic progression is not confirmed, then the subject should resume/continue trial treatment and have their next scan at the regularly scheduled interval. Subjects who obtain a confirmation scan at 4 weeks do not need to undergo the next scheduled imaging assessment if it is due < 4 weeks later. Imaging may be performed at the next scheduled imaging timepoint if the subject remains clinically stable.

NOTE: If a subject with confirmed radiographic progression (i.e. 2 scans at least 28 days apart demonstrating progressive disease) is clinically stable or clinically improved, and there is no further increase in the tumor dimensions at the confirmatory scan, an exception may be considered to continue treatment upon consultation with the Sponsor.

Imaging during the follow-up period is to be repeated every 6 weeks (± 7 days) for the first year patients are on study and then every 9 weeks (± 7 days) after 1 year for subjects who discontinue trial treatment for reasons other than disease progression. Follow-up scans should be continued until the subject experiences confirmed disease progression or starts a new anti-neoplastic therapy.

If imaging assessment beyond the protocol-required imaging time frame is necessary for the subject's continued participation in the follow-up phase of the study, an extended imaging schedule may be considered at the discretion of the investigator. Please refer to Section 6.1-Initial Treatment Phase and Second Course Phase (Retreatment).

7.1.2.7 Tumor Tissue Collection and Correlative Blood Sampling

Subjects with oropharynx cancer must have an assessment of HPV status from tumor tissue (see Section 6.1.1).

All subjects will submit either a "newly obtained" core or excisional biopsy (fine needle aspirate not adequate) to a central lab for characterization of PD-L1 and HPV status, performed retrospectively. Upon receipt of the sample, the central lab will perform an H&E to confirm the sample contains sufficient tumor for PD-L1 analysis. Confirmation of tissue adequacy should be received from the central vendor prior to the first dose of trial treatment. Repeat samples may be required if adequate tissue is not provided.

A "newly obtained" sample may be obtained up to 42 days prior to treatment initiation. Tissue beyond the 42-day window may be considered with Sponsor approval as long as no intervening systemic therapy has been administered. Tissue that has been previously irradiated is acceptable. Subjects for whom newly obtained samples cannot be obtained (e.g. inaccessible or subject safety concern) may submit an archival specimen only upon agreement from the Sponsor.

Submission of tissue in formalin or embedded tumor tissue sample blocks is preferred. If submitting unstained slides, the slides should be freshly cut and submitted to the testing laboratory within 14 days from site slide sectioning date otherwise a new specimen will be requested. Detailed instructions for tissue collection, processing, and shipment are provided in the appendices of the Central Lab Manual.

Blood for correlative biomarker studies should be collected pre-dose Cycle 1, Cycle 2, Cycle 3, and again at treatment discontinuation. Detailed instructions for tissue collection, processing and shipment are provided in the appendices of the Central Lab Manual.

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 patient can be found in the Procedures Manual for the study.

7.1.3.1 Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

Laboratory tests for hematology, chemistry and urinalysis are specified in Table 7.

Table 7 Laboratory Tests

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

[a] Perform on women of childbearing potential only. Serum pregnancy test is preferred but urine test can be considered if serum not appropriate.
[b] If considered standard of care in your region.
[c] Blood Urea Nitrogen is preferred; if not available urea may be tested.

Laboratory tests for screening should be performed within 10 days prior to the first dose of trial treatment. 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/Pharmacodynamic Evaluations

To evaluate the immunogenicity of and exposure to pembrolizumab in this indication, sample collections for analysis of anti-pembrolizumab antibodies (ADA) and PK are currently planned as shown in Section 6.1-Initial Treatment Phase and Second Course Phase (Retreatment).C. Blood samples for PK and ADA that are collected may be only stored at this time. Further analysis may be performed if required. If ongoing PK and/or ADA sampling is deemed unnecessary by the Sponsor, it may be reduced or discontinued.

7.1.3.2.1 Blood Collection for Serum MK-3475

Sample collection, storage and shipment instructions for serum PK samples will be provided in the appendices of the Central Lab Manual.

7.1.3.2.2 Blood Collection for Anti-Pembrolizumab Antibodies

Sample collection, storage and shipment instructions for anti- pembrolizumab (MK-3475) antibody samples will be provided in the appendices of the Central Lab Manual. Anti-pembrolizumab (MK-3475) antibody samples should only be drawn for all study subjects participating in the study.

7.1.3.3 Future Biomedical Research

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

- Leftover DNA
- Leftover tumor tissue

7.1.4 Other Procedures

7.1.4.1 Withdrawal/Discontinuation

When a subject discontinues/withdraws from participation in the trial, all applicable activities scheduled for the end of treatment visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.2 - Assessing and Recording Adverse Events. Subjects who a) attain a CR or b) complete 24 months of treatment with pembrolizumab (MK-3475) may discontinue treatment with the option of restarting treatment if they meet the criteria specified in Section 7.1.5.2.1. After discontinuing treatment following assessment of CR or 24 months of treatment, these subjects should return to the site for a Safety Follow-up Visit (described in Section 7.1.5.3.1) and then proceed to the Follow-up Period of the study (described in Section 7.1.5.3.2).

7.1.4.1.1 Withdrawal From Future Biomedical Research

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

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

7.1.4.2 Blinding/Unblinding

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

7.1.4.3 Calibration of Critical Equipment

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

Critical Equipment for this trial includes:

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

See protocol-specified guidance in the Administrative Binder, and the Central Lab Manual.

7.1.5 Visit Requirements

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

7.1.5.1 Screening

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

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

- Laboratory tests and ECOG PS are to be performed within 10 days prior to the first dose of trial treatment.
- For women of reproductive potential, a serum pregnancy test will be performed within 72 hours prior to the first dose of trial treatment. A urine test may be considered if serum test is not appropriate.
- A "newly obtained" tissue sample is not required to be obtained within 28 days prior to the first dose of trial treatment. The sample should be obtained within 42 days of the first dose. See Section 7.1.2.7 for additional details regarding tumor tissue requirements.

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

7.1.5.2 Treatment Period

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

7.1.5.2.1 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 MK-3475 therapy if they progress after stopping study treatment. This retreatment is termed the Second Course Phase of this study and is only available if the 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
        - Was treated for at least 24 weeks with pembrolizumab (MK-3475) before discontinuing therapy AND
        - Received at least two treatments with pembrolizumab (MK-3475) beyond the date when the initial CR was declared

OR

- Had SD, PR or CR and stopped pembrolizumab (MK-3475) treatment after 24 months of study therapy for reasons other than disease progression or intolerability

AND

- Experienced an investigator-determined confirmed radiographic disease progression after stopping their initial treatment with pembrolizumab (MK-3475)
- Did not receive any anti-cancer treatment since the last dose of pembrolizumab (MK-3475)
- Has a performance status of 0 or 1 on the ECOG Performance Scale
- Demonstrates adequate organ function as detailed in Section 5.1.2
- Female subject of childbearing potential should have a negative serum or urine pregnancy test within 72 hours prior to receiving retreatment with study medication.
- Female subject of childbearing potential should be willing to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study medication (Reference Section 5.7.2). Subjects of child bearing potential are those who have not been surgically sterilized or have been free from menses for > 1 year.
- Male subject should agree to use an adequate method of contraception starting with the first dose of study therapy through 120 days after the last dose of study therapy.
- 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 one additional year.

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

7.1.5.3 Post-Treatment Visits

7.1.5.3.1 Safety Follow-up Visit

The mandatory Safety Follow-Up Visit should be conducted approximately 30 days 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 (MK-3475) (as described in Section 7.1.5.2.1) may have up to two safety follow-up visits, one after the Treatment Period and one after the Second Course Phase.

7.1.5.3.2 Follow-up Visits

Subjects who discontinue trial treatment for a reason other than radiographic disease progression will move into the Follow-Up Phase and should be assessed every 6 weeks (42 ±7 days) by radiologic imaging to monitor disease status. After 1 year, the imaging time point will occur every 9 weeks (±7 days). Every effort should be made to collect information regarding disease status until the start of new anti-cancer therapy, radiographic disease progression, death, end of study or if the subject begins retreatment with pembrolizumab (MK-3475) as detailed in Section 7.1.5.2.1. Information regarding post-study anti-cancer treatment will be collected if new treatment is initiated. If imaging assessment beyond the protocol-required imaging time frame is necessary for the subject's continued participation in the follow-up phase of the study, an extended imaging schedule may be considered at the discretion of the investigator. Please refer to Section 6.1-Initial Treatment Phase and Second Course Phase (Retreatment) .

Subjects who are eligible to receive retreatment with pembrolizumab (MK-3475) according to the criteria in Section 7.1.5.2.1 will move from the Follow-Up Phase to the Second Course Phase when they experience disease progression. Details are provided in Section 6.1.2 – Second Course Phase (Retreatment) for Pembrolizumab (MK-3475).

7.1.5.3.3 Survival Follow-up

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

7.1.5.4 Survival Status

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

7.2 Assessing and Recording Adverse Events

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

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

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

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

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

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

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

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

For this trial, an overdose will be defined as ≥1000 mg (5 times the dose) of pembrolizumab (MK-3475). No specific information is available on the treatment of overdose of pembrolizumab (MK-3475). 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 within 24 hours to the Sponsor either by electronic media or paper. Sponsor Contact information can be found in the Investigator Trial File Binder (or equivalent).

7.2.2 Reporting of Pregnancy and Lactation to the Sponsor

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

Pregnancies and lactations that occur after the consent form is signed but before 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 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. Sponsor Contact information can be found in the Investigator Trial File Binder (or equivalent).

7.2.3 Immediate Reporting of Adverse Events to the Sponsor

7.2.3.1 Serious Adverse Events

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

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

- Is a congenital anomaly/birth defect;
- Is a new cancer (that is not a condition of the study);
- Is associated with an overdose;
- Is an other important medical event

Refer to Table 8 for additional details regarding each of the above criteria.

For the time period beginning when the consent form is signed until 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 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 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 treatment allocation through 90 days following cessation of treatment, any ECI, or follow up to an ECI, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, whether or not related to the Sponsor’s product, must be reported within 24 hours to the Sponsor, either by electronic

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

Events of clinical interest for this trial include:

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

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

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

3. Additional adverse events:

   A separate guidance document has been provided entitled “Event of Clinical Interest Guidance Document” (previously entitled, “Event of Clinical Interest and Immune-Related Adverse Event Guidance Document”). This document can be found in the administrative binder and provides guidance regarding identification, evaluation and management of ECIs and irAEs.

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

7.2.3.3 Protocol-Specific Exceptions to Serious Adverse Event Reporting

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

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

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

7.2.4 Evaluating Adverse Events

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

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

Table 8 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) **or**	
	Is an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours.	
	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	
Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the adverse event cause the Sponsor's product to be discontinued?	
Relationship to test drug	Did the Sponsor's product cause the adverse event? The determination of the likelihood that the Sponsor's product caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the adverse event based upon the available information. **The following components are to be used to assess the relationship between the Sponsor's product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Sponsor's product caused the adverse event (AE):	
	Exposure	Is there evidence that the subject was actually exposed to the Sponsor's product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
	Time Course	Did the AE follow in a reasonable temporal sequence from administration of the Sponsor's product? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors

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

7.2.5 Sponsor Responsibility for Reporting Adverse Events

All Adverse Events will be reported to regulatory authorities, IRB/IECs and investigators in accordance with all applicable global laws and regulations.

8.0 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, but prior to obtaining PD-L1 positivity status, changes are made to primary and/or key secondary hypotheses, or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with ICH Guideline E-9). Changes to exploratory or other non-confirmatory analyses made after the protocol has been finalized, along with an explanation as to when and why they occurred, will be listed in the Clinical Study Report (CSR) for the study. Post hoc exploratory analyses will be clearly identified in the CSR. No separate Statistical Analysis Plan (SAP) will be issued for this study.

8.1 Statistical Analysis Plan Summary

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

The primary purpose of this study is to investigate the safety, tolerability, and anti-tumor activity of pembrolizumab (MK-3475) 200 mg Q3W administered intravenously to subjects with recurrent and/or metastatic head and neck cancer who have failed prior platinum and cetuximab therapy.

8.1.1 Efficacy Analyses

The full analysis set (FAS) population (defined as all subjects with a baseline scan with measurable disease by independent radiology review who receive at least one dose of study treatment) will serve as the primary population for the analyses of efficacy data in this trial. Supportive analyses of efficacy will be conducted in the all Patients as Treated (APaT) population as well as the FAS. Objective response rate will be used to evaluate the primary efficacy hypotheses and will be estimated separately for all subjects and for subjects who are PD-L1 strong positive, where PD-L1 strong positive is defined as PD-L1 tumor proportion score greater than or equal to 50% by IHC. A 97.5% confidence interval along with a one-sided p-value for testing the null hypothesis based on the binomial distribution will be provided for ORR. The respective study is considered to have reached the efficacy objective if the p-value for testing the primary hypothesis in all subjects is less than 1.25% OR if the p-value for testing the primary hypothesis in PD-L1 strong positive subjects is less than 1.25%. A stepdown procedure controls Type I error between the primary PD-L1 strong positive hypothesis and the secondary PD-L1 positive hypothesis. An outline of the efficacy analysis strategy is presented in Table 9 below.

Table 9 Primary Analysis Strategy for Efficacy Endpoints

Endpoint/Variable[+] (Description, Time Point)	Statistical Method	Analysis Population	Missing Data Approach
Primary:			
ORR (RECIST 1.1) based on independent radiology review	Exact test of binomial parameter	FAS	Subjects with missing data are considered non-responders
ORR(RECIST 1.1) in PD-L1 strong positive subjects* based on independent radiology review	Exact test of binomial parameter	FAS	Subjects with missing data are considered non-responders
Secondary:			
ORR(RECIST 1.1) in PD-L1 positive subjects† based on independent radiology review	Exact test of binomial parameter	FAS	Subjects with missing data are considered non-responders
Response Duration based on independent radiology review	Summary statistics using Kaplan-Meier method	All responders	Non-responders are excluded in analysis
Response Duration in PD-L1 strong positive subjects based on independent radiology review	Summary statistics using Kaplan-Meier method	All responders among PD-L1 strong positive* subjects	Non-responders are excluded in analysis
Response Duration in PD-L1 positive subjects based on independent radiology review	Summary statistics using Kaplan-Meier method	All responders among PD-L1 positive† subjects	Non-responders are excluded in analysis
ORR (modified RECIST 1.1) in all subjects, all PD-L1 positive subjects, and all PD-L1 strong positive subjects	Point estimate and 95% CI using exact binomial methods	FAS	Subjects with missing data are considered non-responders
ORR (RECIST 1.1) in HPV positive subjects	Point estimate and 95% CI using exact binomial methods	FAS	Subjects with missing data are considered non-responders
Progression-free survival in all subjects, all PD-L1 positive subjects, and all PD-L1 strong positive subjects	Summary statistics using Kaplan-Meier method	FAS	Censored at last assessment
Overall survival in all subjects , all PD-L1 positive subjects, and all PD-L1 strong positive subjects	Summary statistics using Kaplan-Meier method	FAS	Censored at last assessment
* PD-L1 strong positive is defined as PD-L1tumor proportion score ≥50% by IHC. †PD-L1 positive is defined as PD-L1tumor proportion score exceeding 0% by IHC.			

8.1.2 Safety Analyses

The All-Patients-as-Treated population will be employed for safety analyses.

8.1.3 Power and Sample Size

Assuming that approximately 135 of the 150 enrolled subjects with recurrent and/or metastatic head and neck cancer will be evaluable for the primary efficacy analysis in the FAS population, the study has approximately 85% power to demonstrate that the ORR is >5% with a type I error rate of 1.25% [redacted] Success for this hypothesis requires at least 14/135 responses.

Assuming that the prevalence of PD-L1 strong positive subjects with recurrent and/or metastatic head and neck cancer is 20%~30%, then among the 150 enrolled subjects approximately 30~45 PD-L1 strong positive subjects would be expected. The study has approximately 92% to 99% power to demonstrate that the ORR >5% with a type I error rate of 1.25% if the [redacted] Success for this hypothesis requires at least 6 responses out of 30~39 PD-L1 strong positive subjects, and at least 7 responses out of 40~45 PD-L1 strong positive subjects.

8.1.4 Interim Analysis

No interim analyses are planned.

8.2 Statistical Analysis Plan

8.2.1 Responsibility for Analyses/In-House Blinding

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

This trial is being conducted as an open-label non-randomized single-arm clinical trial, i.e., subjects, investigators, and Sponsor personnel will be aware of subject treatment assignments after each subject is enrolled and treatment is assigned. The study team at the Sponsor consisting of clinical, statistical, scientific programming and data management personnel, will be blinded to individual-level PD-L1 biomarker results until the time that a study report is written. While the study team is blinded to the PD-L1 patient-level biomarker results, an unblinded Sponsor statistician and Sponsor statistical programmer who will have access to the PD-L1 results for the purpose of data review and cleaning and will have no other responsibilities associated with the study. Summary reports of biomarker prevalence may be provided to the study team at the Sponsor by the IVRS vendor, the unblinded Sponsor statistician, and/or an unblinded external statistician.

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

8.2.2 Hypotheses/Estimation

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

8.2.3 Analysis Endpoints

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

8.2.3.1 Efficacy/Immunogenicity/Pharmacokinetics Endpoints

The primary efficacy endpoint is objective response rate (ORR), defined as the proportion of subjects in the analysis population who have complete response (CR) or partial response (PR) using RECIST 1.1 criteria at any time during the study. Response for the primary analyses will be determined by independent radiology review. ORR will be evaluated separately in all subjects and the subset of all PD-L1 strong positive subjects (defined as a PD-L1 tumor proportion score ≥50% by IHC).

Supportive analyses of ORR will be performed based on site assessments using RECIST 1.1.

ORR in all subjects with any PD-L1 positive will be a key secondary efficacy endpoint. PD-L1 positivity is defined as PD-L1 tumor proportion score >0% by IHC. Other key secondary efficacy endpoints that will be evaluated in all subjects, all PD-L1 positive subjects, and all PD-L1 strong positive subjects include:

Duration of Response: defined as time from first RECIST 1.1 response to disease progression in subjects who achieve a PR or better

ORR by modified RECIST 1.1: defined as proportion of subjects with a CR or PR using modified RECSIT 1.1 criteria as defined in Section 4.2.3.1.

ORR among HPV positive subjects: defined as the proportion of subjects with HPV positive tumor biopsy who achieve a CR or PR according to RECIST 1.1 criteria.

Progression-free survival (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.

Overall survival (OS): defined as the time from allocation to death due to any cause.

Additional exploratory endpoints include PFS by modified RECIST 1.1 criteria and ORR/PFS/OS by exploratory candidate biomarkers.

8.2.3.2 Safety Endpoints

A description of safety measures is provided in Section 4.2.3.2.

The primary safety endpoints are AEs graded using CTCAE (Version 4.0) criteria. Safety will be assessed by quantifying the toxicities and grades experienced by subjects who have received pembrolizumab (MK-3475), including serious adverse events (SAEs) and events of

clinical interest (ECIs). Immune-related ECIs, as described in Section 7.2.3.2 will be collected. Other safety endpoints include laboratory safety assessments, ECOG performance status, vital signs and physical examinations.

8.2.4 Analysis Populations

8.2.4.1 Efficacy Analysis Populations

The Full Analysis Set (FAS) population will serve as the primary population for the analysis of efficacy data in this study. The FAS population consists of all subjects who:

- Receive at least one dose of study treatment,
- Have a baseline scan with measurable disease per RECIST 1.1 by independent radiology review

A supportive analysis using the All Patients as Treated (APaT) population, defined as all enrolled subjects who receive at least one dose of study medication, will be performed for the primary efficacy endpoint(s). Supportive analyses in the FAS population using the site radiology assessment will require baseline scan with measureable disease per RECIST 1.1 using site radiology assessment.

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

8.2.4.2 Safety Analysis Populations

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

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

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

8.2.5 Statistical Methods

Statistical testing and inference for safety analyses are described in 8.2.5.2. Efficacy results that will be considered to be statistically significant after consideration of the strategy for controlling the Type I error are described in Section 8.2.6, Multiplicity. Nominal p-values may be computed for other efficacy analyses as a measure of strength of association between the endpoint and the treatment effect rather than formal tests of hypotheses.

8.2.5.1 Statistical Methods for Efficacy Analyses

For the primary efficacy endpoint independently reviewed ORR using RECIST 1.1, the point estimate, 97.5% confidence interval, and p-value for testing ORR is greater than the

historical control rate of 5% will be provided separately for all subjects and PD-L1 strong positive subjects using exact binomial distribution. Subjects in the primary analysis population (FAS) without response data will be counted as non-responder.

Efficacy for the key secondary endpoint of ORR among PD-L1 positive subjects, as well as other secondary analyses of ORR using modified RECIST 1.1 and ORR among subjects with HPV positive head and neck cancer will be evaluated in the same manner as in the primary analysis.

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

The primary analysis for each hypothesis will be conducted after all subjects have at least 6 months of follow-up. The final analysis of OS will occur when <5% of patients remain on study drug.

Table 10 summarizes the key efficacy analyses.

Table 10 Analysis Strategy for Key Efficacy Variables

Endpoint	Statistical Method	Analysis Population	Missing data approach
ORR • RECIST 1.1, independent radiology review	Exact test of binomial parameter	FAS in all below populations: • all-comers • PD-L1 strong positive* • PD-L1 positive‡	Subjects with missing data are considered non-responders
ORR • RECIST 1.1, independent radiology review • modified RECIST 1.1, independent radiology review • modified RECIST 1.1, investigator	Point estimate and exact binomial CI‖	FAS in all below populations: • all-comers • PD-L1 strong positive* • PD-L1 positive‡ • HPV positive APaT in all below populations: • all-comers • PD-L1 strong positive • PD-L1 any positive • HPV positive	Subjects with missing data are considered non-responders
Response Duration • RECIST 1.1, independent radiology review • modified RECIST 1.1, investigator	Summary statistics using Kaplan-Meier method	FAS in all below populations: • all-comers • PD-L1 strong positive* • PD-L1 positive‡ APaT in all below populations: • all-comers • PD-L1 strong positive • PD-L1 positive	Non-responders are excluded in analysis

Endpoint	Statistical Method	Analysis Population	Missing data approach
PFS • RECIST 1.1, independent radiology review • modified RECIST 1.1, investigator	Summary statistics using Kaplan-Meier method	FAS in all below populations: • all-comers • PD-L1 strong positive* • PD-L1 positive‡ APaT in all below populations: • all-comers • PD-L1 strong positive • PD-L1 positive	Censored at last assessment date
OS • RECIST 1.1, independent radiology review • modified RECIST 1.1, investigator	Summary statistics using Kaplan-Meier method	FAS in all below populations: • all-comers • PD-L1 strong positive* • PD-L1 positive‡ APaT in all below populations: • all-comers • PD-L1 strong positive • PD-L1 positive	Censored at last assessment date
* PD-L1 strong positive is defined as PD-L1tumor proportion score ≥50% by IHC. ‡ PD-L1 positive is defined as PD-L1tumor proportion score exceeding 0% by IHC. ‖ Exact Clopper-Pearson 95% CI will be provided.			

Exploratory analyses of PFS using modified RECIST 1.1 criteria and PFS/OS by exploratory candidate biomarkers will also follow the same approach as for the secondary analyses of PFS and OS. The exploratory analysis of ORR by PD-L1 combined positive score (CPS) and exploratory candidate biomarkers will be conducted using point estimate and exact binomial CI.

8.2.5.2 Statistical Methods for Safety Analyses

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

Summary statistics (counts, percentage, mean, standard deviation, etc.) will be provided for the safety endpoints as appropriate. The 95% confidence interval for the incidence rate of Grade 2 or higher adverse events with an immune etiology and the incidence rate of Grade 4/5 AEs will be provided as appropriate.

8.2.5.3 Summaries of Baseline Characteristics, Demographics, and Other Analyses

8.2.5.3.1 Demographic and Baseline Characteristics

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

8.2.5.3.2 Pharmacokinetic Analyses

Based on pharmacokinetic data obtained within this study, the exposure response relationship for MK-3475 and measures of antitumor activity/efficacy and pharmacodynamic biomarkers may be explored. The analysis, if performed, will be reported separately.

8.2.6 Multiplicity

The false positive rate for testing the primary efficacy hypotheses is controlled at 2.5% (1-sided) with 1.25% allocated to all subjects and 1.25% allocated to PD-L1 strong positive subjects. The key secondary efficacy hypothesis of ORR based on RECIST 1.1 assessed by independent radiology review in PD-L1 positive subjects will be tested at 1.25% (one-sided) if the primary efficacy hypothesis in PD-L1 strong positive subjects is rejected. If both the primary hypothesis for PD-L1 strong positive subjects and the key secondary efficacy hypothesis are rejected, the additional alpha level 1.25% will be allocated back to all subjects and the primary efficacy hypothesis for all subjects will be tested at 2.5% (Figure 2).

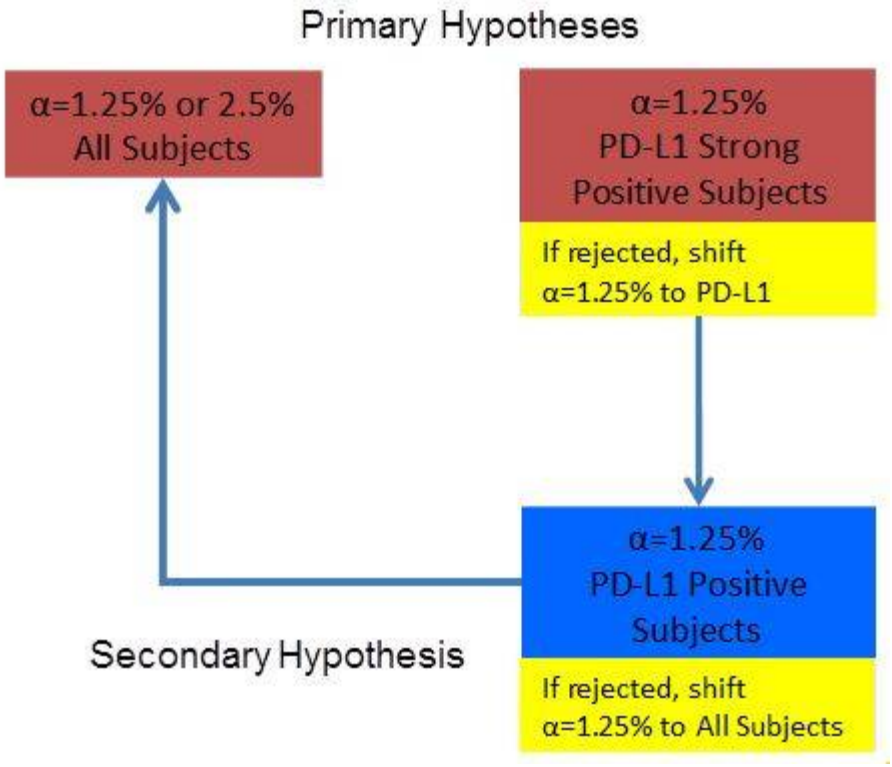

Figure 2 Multiplicity Strategy

8.2.7 Sample Size and Power Calculations

Assuming that approximately 135 of the 150 enrolled subjects with recurrent and/or metastatic head and neck cancer will be evaluable for the primary efficacy analysis in the FAS population, the study has approximately 85% power to demonstrate that the ORR is >5% with a type I error rate of 1.25% [redacted] Success for this hypothesis requires at least 14/135 responses. The null ORR rate of 5% was determined based on a prior randomized trial of methotrexate therapy vs. gefinitib in a second line population in which an ORR of 4% was observed in the methotrexate arm [28].

The proportion of subjects who are PD-L1 strong positive among the 150 subjects enrolled is not known but is estimated to be approximately 20%~30%, then 150 subjects would be expected to provide 30~45 PD-L1 strong positive subjects with recurrent and/or metastatic head and neck cancer will be evaluable for the primary efficacy analysis in the FAS population. Figure 3 shows the power curve ranging about 92% to 99% vs the sample size between 30 and 45, when the ORR>5% with a type I error rate of 1.25% [redacted] Success for this hypothesis requires at least 6 responses out of 30~39 subjects with PD-L1 strongly positive, and at least 7 responses out of 40~45 subjects with PD-L1 strongly positive. The power may increase or decrease depending on the actual number of PD-L1 strong positive subjects who are enrolled in the study (Figure 3).

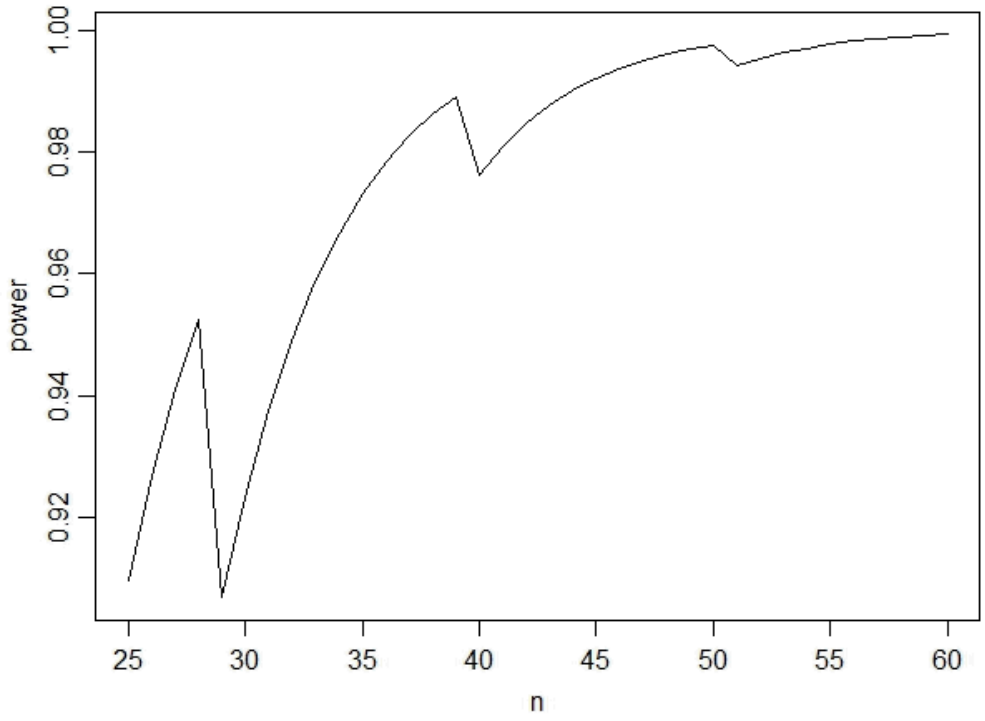

Figure 3 Power Curve vs Sample Size of PD-L1 Strong Positive Subjects

8.2.8 Subgroup Analyses and Effect of Baseline Factors

All efficacy endpoints will be evaluated by the following categories:

- HPV-positive and HPV-negative subjects
- PD-L1 positive (> 0%) and PD-L1 negative subjects.
- PD-L1 strong positive (≥50%) and PD-L1 not strong positive (0 to <50%).

In addition, subgroup analyses of efficacy (ORR, PFS and OS) by the following demographic factors will be performed.

- Baseline ECOG status
- Number of prior therapies

8.2.9 Interim Analyses

No interim analyses are planned in this trial.

8.2.10 Compliance (Medication Adherence)

A day within the study will be considered an On-Therapy day if the subject receives the study medication infusion. The number of Days on Therapy is the total number of days from the first day of study medication to the date of the last dose of study medication.

Summary statistics for the number of Days on Therapy will be provided by treatment group for the FAS population.

8.2.11 Extent of Exposure

Extent of Exposure for a subject is defined as number of cycles in which the subject receives the study medication infusion. Summary statistics will be provided on Extent of Exposure for APaT 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 11.

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 11 Product Descriptions

Product Name & Potency	Dosage Form
Pembrolizumab (MK-3475) 100 mg / 4 mL	Solution for Infusion

9.2 Packaging and Labeling Information

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

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

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

10.1 Confidentiality

10.1.1 Confidentiality of Data

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

10.1.2 Confidentiality of Subject Records

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

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

10.1.3 Confidentiality of Investigator Information

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

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

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

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

10.1.4 Confidentiality of IRB/IEC Information

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

10.2 Compliance with Financial Disclosure Requirements

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

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

10.3 Compliance with Law, Audit and Debarment

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

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

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

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

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

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

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

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

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

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

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

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

10.4 Compliance with Trial Registration and Results Posting Requirements

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

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

10.5 Quality Management System

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

10.6 Data Management

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

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

10.7 Publications

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

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

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

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

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

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12.0 APPENDICES

12.1 Merck Code of Conduct for Clinical Trials

Merck*
Code of Conduct for Clinical Trials

I. Introduction

A. Purpose

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

B. Scope

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

II. Scientific Issues

A. Trial Conduct

1. Trial Design

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

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

2. Site Selection

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

3. Site Monitoring/Scientific Integrity

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

B. Publication and Authorship

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

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

III. Subject Protection

A. IRB/ERC review

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

B. Safety

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

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

C. Confidentiality

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

D. Genomic Research

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

IV. Financial Considerations

A. Payments to Investigators

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

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

B. Clinical Research Funding

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

C. Funding for Travel and Other Requests

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

V. Investigator Commitment

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

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

12.2 Collection and Management of Specimens for Future Biomedical Research

1. Definitions

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

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

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

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research

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

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

3. Summary of Procedures for Future Biomedical Research

a. Subjects for Enrollment

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

b. Informed Consent

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

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

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

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

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

c. eCRF Documentation for Future Biomedical Research Specimens

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

d. Future Biomedical Research Specimen Collections

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

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

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

4. Confidential Subject Information for Future Biomedical Research

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

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

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

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

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

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

5. Biorepository Specimen Usage

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

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

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

6. Withdrawal From Future Biomedical Research

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

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

7. Retention of Specimens

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

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

8. Data Security

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

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

9. Reporting of Future Biomedical Research Data to Subjects

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

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

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

10. Gender, Ethnicity and Minorities

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

11. Risks Versus Benefits of Future Biomedical Research

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

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

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

12. Self-Reported Ethnicity

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

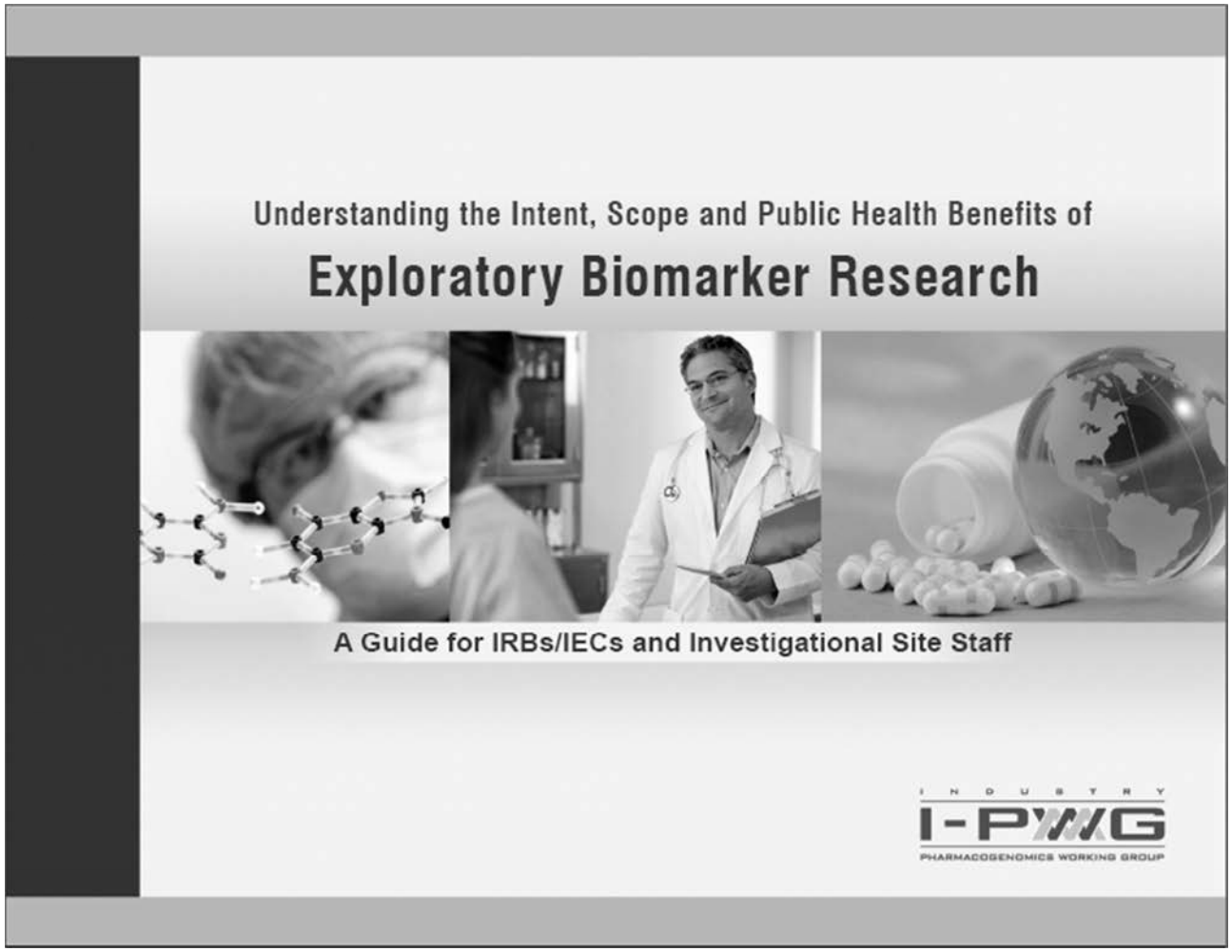
13. Questions

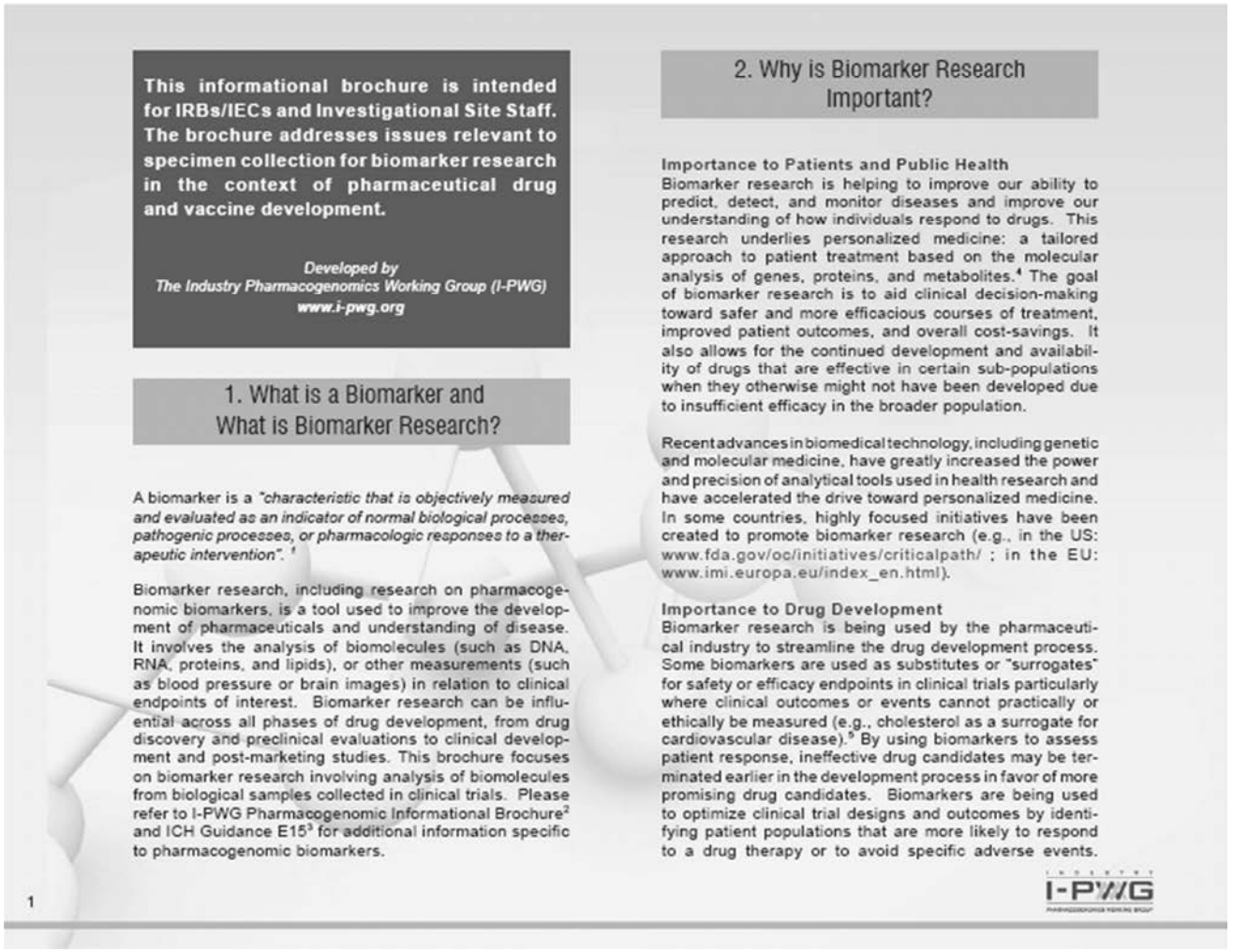
Any questions related to the future biomedical research should be e-mailed directly to clinical.specimen.management@merck.com.

14. References

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

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





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

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

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

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

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

2. Why is Biomarker Research Important?

Importance to Patients and Public Health

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

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

Importance to Drug Development

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

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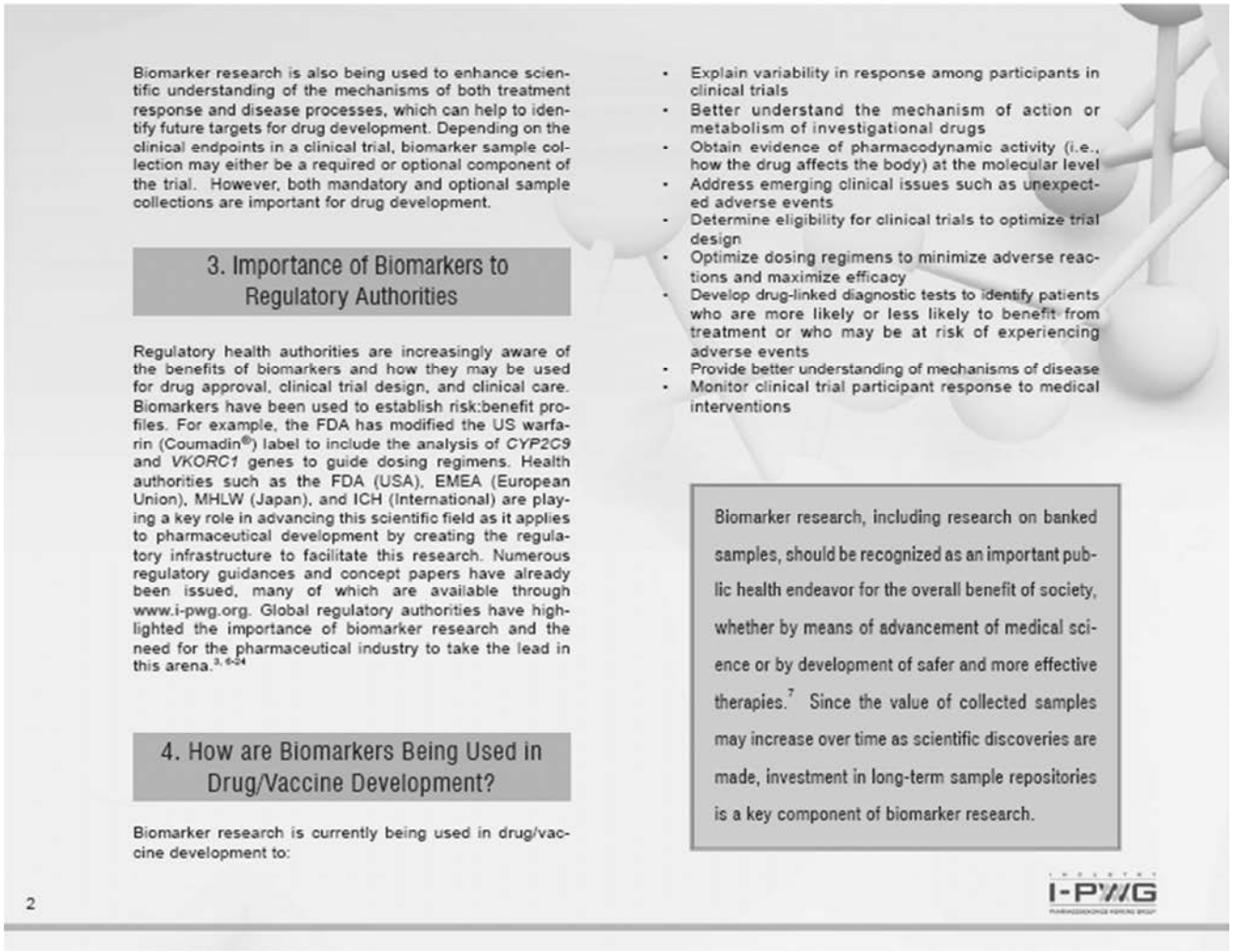
Biomarker research is also being used to enhance scientific understanding of the mechanisms of both treatment response and disease processes, which can help to identify future targets for drug development. Depending on the clinical endpoints in a clinical trial, biomarker sample collection may either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

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

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

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

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

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

6. Biomarker Samples from Clinical Trials: An Invaluable Resource

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

7. Informed Consent for Collection & Banking of Biomarker Samples

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

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

Optional vs. Required Subject Participation

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

Consent for Future Research Use

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

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

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

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

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

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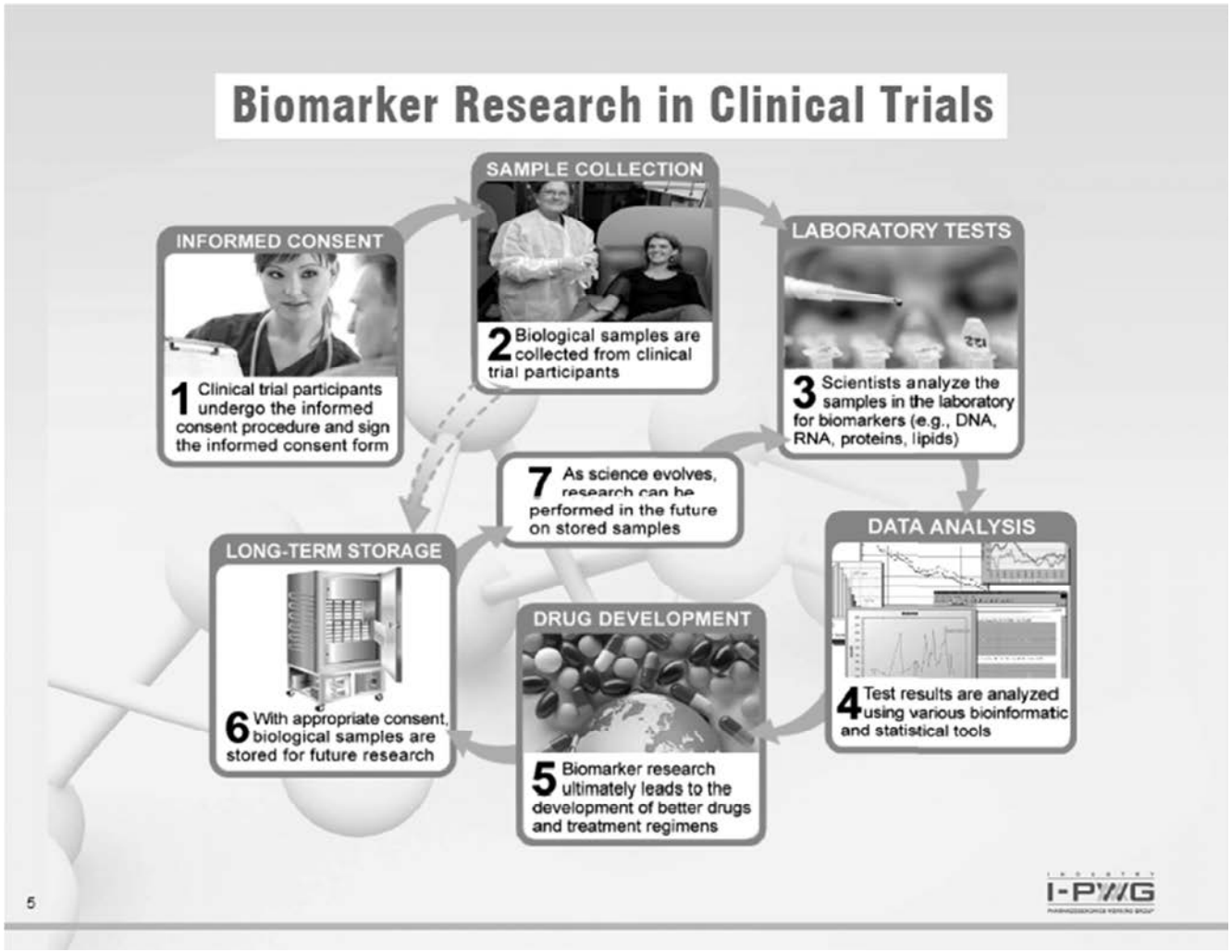
Biomarker Research in Clinical Trials
SAMPLE COLLECTION
2 Biological samples are collected from clinical trial participants
LABORATORY TESTS
3 Scientists analyze the samples in the laboratory for biomarkers (e.g., DNA, RNA, proteins, lipids)
INFORMED CONSENT
1 Clinical trial participants undergo the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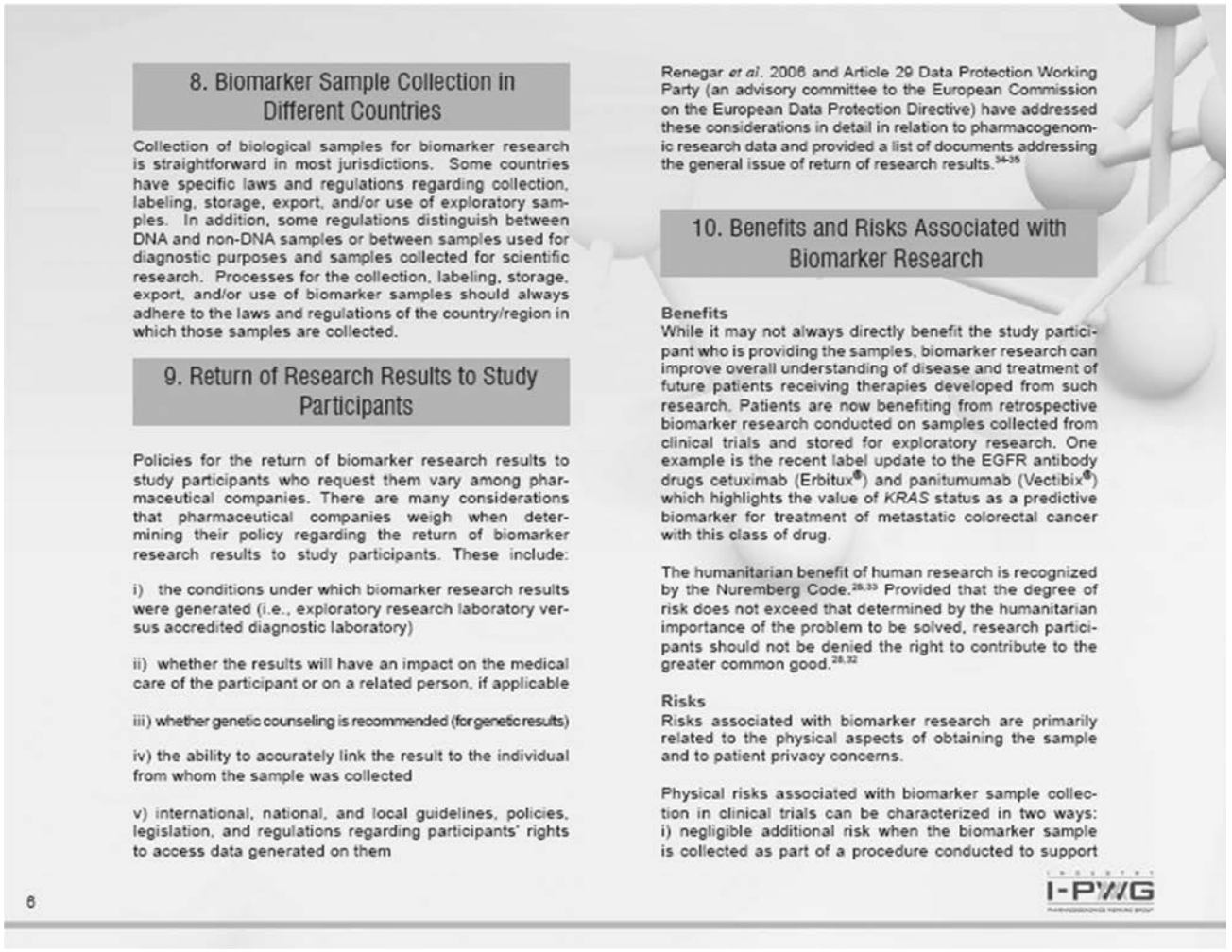

8. Biomarker Sample Collection in Different Countries

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

9. Return of Research Results to Study Participants

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

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

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

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

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

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

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

10. Benefits and Risks Associated with Biomarker Research

Benefits

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

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

Risks

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

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

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

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

11. Privacy, Confidentiality, and Patient Rights

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

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

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

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

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

12.Where to Get More Information?

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

13. What is I-PWG?

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

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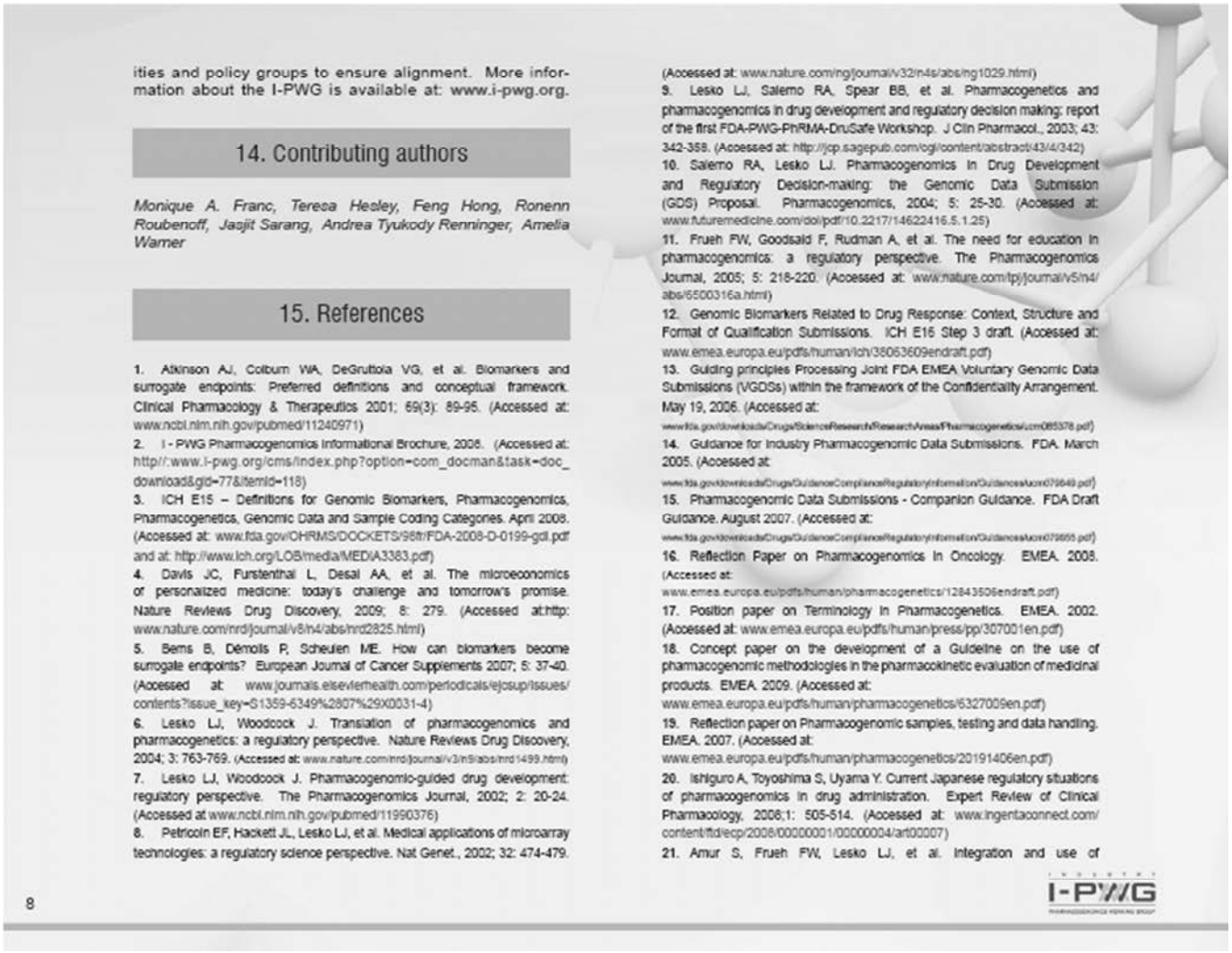

ities and policy groups to ensure alignment. More information about the I-PWG is available at: www.i-pwg.org.

14. Contributing authors

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I-PWG


www.i-pwg.org

12.4 Abbreviations

Abbreviation/Term	Definition
1L	First Line
2L	Second Line
AE	Adverse Event
ADA	Anti-Drug Antibodies
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
AP	Alkaline Phosphatase
APaT	All Patients as Treated
aPTT	Activated Partial Thromboplastin Time
ASCO	American Society of Clinical Oncology
AST	Aspartate Aminotransferase
ß-HCG	Beta Human Chorionic Gonadotropin
BSA	Body Surface Area
CBC	Complete Blood Count
CI	Confidence Interval
CNS	Central Nervous System
CPS	Combined Positive Score
CR	Complete Response
CrCl	Calculated Creatinine Clearance
CRF	Case Report Form
CSR	Clinical Study Report
CT	Computed Tomography
CTCAE	Common Toxicity Criteria for Adverse Events
CTLA-4	Cytotoxic T-Lymphocyte-Associated Antigen-4
DNA	Deoxyribonucleic acid
DR	Drug Related
ECI	Events of Clinical Interest
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Forms
EORTC	European Organisation for Research and Treatment of Cancer
ePRO	Electronic Patient Reported Outcomes
ERC	Ethics Review Committee
FBR	Future Biomedical Research
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FDAMA	Food and Drug Administration Modernization Act
FNA	Fine Needle Aspirate
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
HBsAg	Hepatitis B surface Antigen
HCV	Hepatitis C Virus
HEA	Health Economic Assessment
HIV	Human Immunodeficiency Virus
HNSCC	Head and Neck Squamous Cell Carcinoma
HPV	Human Papillomavirus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization

Abbreviation/Term	Definition
IHC	Immunohistochemistry
INR	International Normalized Ratio
irAEs	Immune-related Adverse Events
IRB	Institutional Review Board
ITIM	Immunoreceptor Tyrosine-based Inhibition Motif
ITSM	Immunoreceptor Tyrosine-based Switch Motif
ITT	Intention To Treat
IV	Intravenous
IVRS	Interactive Voice Response System
IWRS	Integrated Web Response System
Kg	Kilogram
LDH	Lactate Dehydrogenase
mAb	Monoclonal Antibody
mcL	Microliters
MEL	Melanoma
Mg	Milligram
Mg/kg	Milligram per Kilogram
mL	milliliter
MRI	Magnetic Resonance Imaging
MSD	Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
MTD	Maximum Tolerated Dose
NA or N/A	Not Applicable
NCI	National Cancer Institute
NSAID	Non-Steroidal Anti-inflammatory Drug
NSCLC	Non-Small Cell Lung Cancer
ORR	Objective Response Rate
ORST	Oncologic Response-Solid Tumor
OS	Overall Survival
OTC	Over-the-counter
PD	Progressive Disease
PFS	Progression Free Survival
PGt	Pharmacogenetic
PIN	Personal Identification Number
PK	Pharmacokinetic
PK-PD	Pharmacokinetic-Pharmacodynamic
PO	Oral Administration
PR	Partial Response
PT	Prothrombin Time
PS	Performance Status
QoL	Quality of Life
R/M	Recurrent or Metastatic
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic Acid
RR	Response Rate
Q2W	Every 2 Weeks
Q3W	Every 3 Weeks
SAE	Serious Adverse Events
SAP	Statistical Analysis Plan
SFU	Survival Follow-Up
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase

Abbreviation/Term	Definition
SOC	Standard of Care
SOP	Standard Operating Procedures
TIL	Tumor Infiltrating Lymphocytes
TPS	Tumor Proportion Score
TSH	Thyroid Stimulating Hormone
ULN	Upper Limit of Normal
WBC	White Blood Cell

12.5 ECOG Performance Status

GRADE	ECOG PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self care but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited self care; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any self care; totally confined to bed or chair
5	Dead

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

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

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

* As published in the European Journal of Cancer:

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.

13.0 SIGNATURES

13.1 Sponsor's Representative

TYPED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	

13.2 Investigator

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

TYPED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	