Official Protocol Title:	A Phase III Randomized Trial of MK-3475 (Pembrolizumab) versus Standard Treatment in Subjects with Recurrent or Metastatic Head and Neck Cancer
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TITLE:

A Phase III Randomized Trial of MK-3475 (Pembrolizumab) versus Standard Treatment in Subjects with Recurrent or Metastatic Head and Neck Cancer

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DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
3475-040-14	03-Nov-2021	Added language to allow participants to rollover to a pembrolizumab extension study
3475-040-13	21-Apr-2021	To update the dose modification and toxicity management guidelines for irAEs.
3475-040-12	12-Jan-2018	Added guidelines for management of myocarditis.
3475-040-11	02-Nov-2016	Updated statistics section survival follow-up for conducting the primary efficacy analysis.
3475-040-10	10-Mar-2016	Decreased sample size due to higher prevalence of a biomarker group during enrollment.
3475-040-09	04-Mar-2016	Decreased sample size due to higher prevalence of a biomarker group during enrollment and updated statistics.
3475-040-08	16-Jul-2015	Updated methotrexate dose modifications to current SmPC.
3475-040-07	03-Apr-2015	Increased sample size to allow for PD-L1formal testing.
3475-040-06	16-Mar-2015	Increased sample size to allow formal PD-L1 testing and updated statistics.
3475-040-05	23-Mar-2015	Increased sample size to allow formal PD-L1 testing and updated statistics.
3475-040-04	02-Jan-2015	Revised imaging frequency in response to Germany HA.

Document	Date of Issue	Overall Rationale
3475-040-03	26-Jan-2015	Revised contraception language and dose modification language in response to France HA.
3475-040-02	14-Dec-2014	Revised dose modification language in response to MHRA.
3475-040-01	27-Feb-2015	Increased sample size to allow formal PD-L1 testing and updated statistics.
3475-040-00	01-Aug-2014	NA

SUMMARY OF CHANGES

PRIMARY REASON(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
1.0	Trial Summary	Once subjects have achieved the trial objective or the trial has ended, subjects are discontinued from the trial and may be enrolled in an extension trial to continue protocol-defined assessments and treatment	This trial has been identified to rollover into an extension trial
2.2	Trial Diagram	Pembrolizumab extension trial after survival follow-up is added to the diagram	
5.10	Beginning and End of the Trial	Added that upon trial completion, subjects are discontinued and may be enrolled in a pembrolizumab extension trial	

ADDITIONAL CHANGE(S) FOR THIS AMENDMENT:

Section Number-(s)	Section Title-(s)	Description of Change-(s)	Rationale
1.0 5.1.2 5.10 6.1.1 6.1.2 7.1.1.1.2 7.1.1.3	Trial Summary Participant Inclusion Criteria Beginning and End of Trial Pembrolizumab Arm Standard Treatment Arm-Subjects Receiving Methotrexate, Docetaxel, or Cetuximab Consent and Collection of Specimens for Future Biomedical Research Subject Identification Card	Revised informed consent language to allow for documented informed consent	To allow for operational changes needed to accommodate the COVID-19 pandemic and its impact on the informed consent process
5.5.2	Prohibited Concomitant Medications	Added a note that any COVID-19 vaccine that is licensed in a given country is allowed in the study	To clarify the concomitant use of COVID-19 vaccines
6.1.1	Pembrolizumab Arm	Corrected format of superscripts within the trial flow chart table	For clarity
Overall	Overall	Minor editorial/spelling and formatting changes	For clarity

1.0 TRIAL SUMMARY

Abbreviated Title	Ph 3 Trial of MK-3475 (Pembrolizumab) vs. Standard Treatment in Recurrent/Metastatic Head and Neck Cancer
Trial Phase	Phase III
Clinical Indication	Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma
Trial Type	Interventional
Type of control	Active Control without Placebo
Route of administration	Intravenous
Trial Blinding	Unblinded Open-label
Treatment Groups	MK-3475 (also known as pembrolizumab) 200 mg every 3 weeks Standard Treatment: Methotrexate 40 mg/m^2 once weekly (may be increased to a maximum of 60 mg/m^2 weekly in the absence of toxicity) or Docetaxel 75 mg/m^2 once every 3 weeks or Cetuximab 400 mg/m^2 loading dose and then 250 mg/m^2 weekly
Number of trial subjects	Approximately 466 subjects will be enrolled.
Estimated duration of trial	The sponsor estimates that the trial will require approximately 24 months from the time the first subject signs the informed consent until the last subject's last visit.
Duration of Participation	Each subject will participate in the trial until death, discontinuation from the trial, or lost-to-follow-up from the time the subject provides documented informed consent through the final contact. After a screening phase of 28 days, each subject will receive treatment based on the arm to which they have been randomized. Treatment on trial will continue until disease progression is verified by the central imaging vendor, unacceptable adverse event(s), intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw the subject, noncompliance with trial treatment or procedures requirements, receives 24 months of study medication (pembrolizumab arm only), or administrative reasons. Subjects on the pembrolizumab arm who attain a complete response may consider stopping trial treatment if they meet criteria for holding therapy. Subjects receiving pembrolizumab who stop trial treatment after receiving 24 months of study medication for reasons other than disease progression or intolerability, or subjects who attain a complete response and stop trial treatment may be eligible for up to one year of retreatment upon experiencing disease progression. The decision to retreat will be at the discretion of the investigator only if they meet the criteria for retreatment and the trial is ongoing. After the end of treatment, each subject will be followed for 30 days for adverse event monitoring (serious adverse events [SAEs] will be collected for 90 days after the end of treatment). Subjects who discontinue for reasons other than disease progression will have post-treatment follow-up for disease status until disease progression, initiating a non-study cancer treatment, withdrawing consent, or becoming lost to follow-up. All subjects will be followed by telephone for overall survival until death, withdrawal of consent, or the end of the study.

	Once the subject has achieved the trial objective or the trial has ended, the subject is discontinued from the trial and may be enrolled in an extension trial to continue protocol-defined assessments and treatment.
Randomization Ratio	1:1

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

2.0 TRIAL DESIGN

2.1 Trial Design

This is a randomized, active-controlled, multi-site, open-label trial of pembrolizumab in subjects with advanced head and neck cancer to be conducted in conformance with Good Clinical Practices.

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

This trial will use an adaptive design based on pre-specified criteria, using an independent, external Data Monitoring Committee (DMC) to monitor safety and efficacy.

2.2 Trial Diagram

The trial design is depicted in Figure 1.

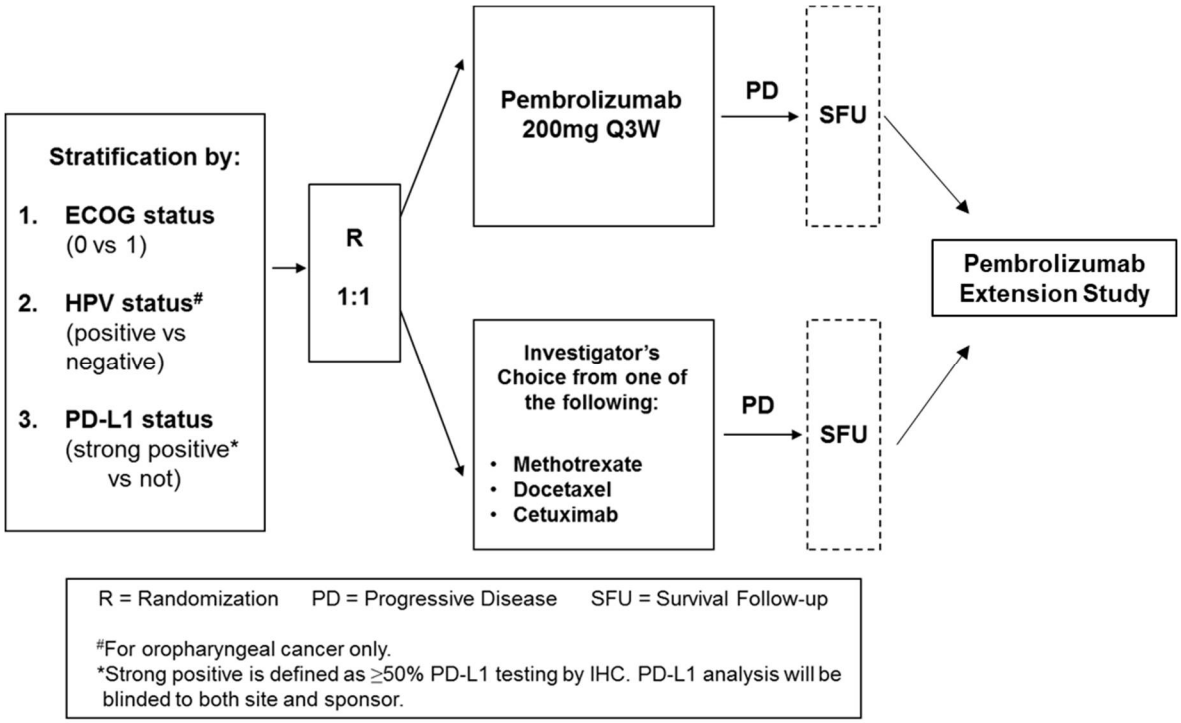

Figure 1 Trial Diagram.

3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

3.1 Primary Objective(s) & Hypothesis(es)

All Subjects

Objective: To compare the overall survival (OS) in subjects with R/M HNSCC treated with pembrolizumab compared to standard treatment.

Hypothesis (H1): Pembrolizumab prolongs OS in subjects with R/M HNSCC compared to standard treatment.

3.2 Secondary Objective(s) & Hypothesis(es)

Key Secondary Objectives & Hypotheses

PD-L1 Positive Population: Subjects with PD-L1 positive expression defined by ≥1% Combined Positive Score (CPS), henceforth abbreviated as PD-L1 1% CPS

Objective: To compare Overall Survival (OS) in subjects with R/M HNSCC treated with pembrolizumab compared to standard treatment.

Hypothesis (H2): Pembrolizumab prolongs OS in subjects with R/M HNSCC compared to standard treatment.

Objective: To compare ORR per RECIST 1.1 as assessed by blinded independent radiology review in subjects with R/M HNSCC treated with pembrolizumab compared to standard treatment.

Hypothesis (H4): Pembrolizumab increases ORR per RECIST 1.1 by blinded independent radiology review in subjects with R/M HNSCC compared to standard treatment.

Objective: To compare PFS per RECIST 1.1 as assessed by blinded independent radiology review in subjects with R/M HNSCC treated with pembrolizumab compared to standard treatment.

Hypothesis (H6): Pembrolizumab prolongs PFS per RECIST 1.1 by blinded independent radiology review in subjects with R/M HNSCC compared to standard treatment.

All Subjects (regardless of PD-L1 expression)

Objective: To compare ORR per RECIST 1.1 as assessed by blinded independent radiology review in subjects with R/M HNSCC treated with pembrolizumab compared to standard treatment.

Hypothesis (H3): Pembrolizumab increases ORR per RECIST 1.1 by blinded independent radiology review in subjects with R/M HNSCC compared to standard treatment.

Objective: To compare PFS per RECIST 1.1 as assessed by blinded independent radiology review in subjects with R/M HNSCC treated with pembrolizumab compared to standard treatment.

Hypothesis (H5): Pembrolizumab prolongs PFS per RECIST 1.1 by blinded independent radiology review in subjects with R/M HNSCC compared to standard treatment.

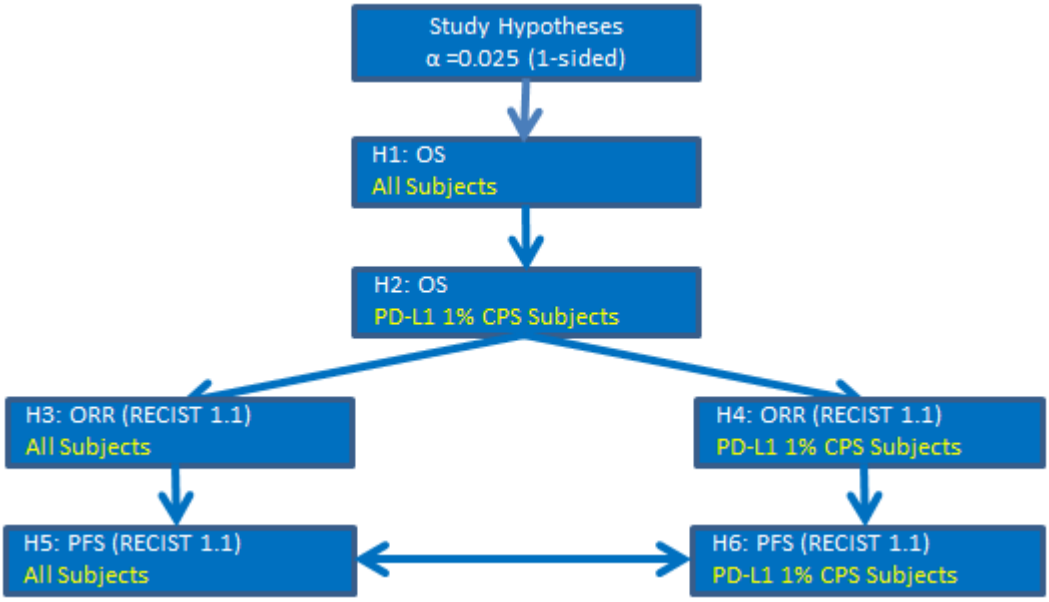

Figure 2 Primary and Key Secondary Hypotheses

Other Secondary Objectives & Hypotheses

The following objectives will be evaluated separately among (1) **Subjects with PD-L1 1% CPS** and (2) **All Subjects Regardless of PD-L1 Expression**.

Objective: To evaluate the safety and tolerability profile of pembrolizumab.

Objective: To evaluate Time to Progression (TTP) per RECIST 1.1 and Duration of Response (DOR) per RECIST 1.1 by blinded independent radiology review in subjects with R/M HNSCC treated with pembrolizumab compared to standard treatment.

Objective: To evaluate PFS per modified RECIST by blinded independent radiology review in subjects with R/M HNSCC treated with pembrolizumab compared to standard treatment.

3.3 Exploratory Objectives

1) **Objective:** To compare OS, PFS per RECIST 1.1 as assessed by blinded independent radiology review, and ORR per RECIST 1.1 as assessed by blinded independent radiology review in subjects with strongly positive PD-L1 expression defined by ≥ 50% TPS in R/M HNSCC treated with pembrolizumab compared to standard treatment.

2) **Objective:** To evaluate changes in health-related quality-of-life assessments from baseline in subjects with R/M HNSCC using the EORTC QLQ C-30 and EORTC QLQ-H&N35.

3) **Objective:** To characterize utilities in previously-treated subjects with R/M HNSCC cancer using the EuroQol EQ-5D.

4) **Objective**: To investigate the relationship between pembrolizumab treatment and biomarkers predicting response (e.g., PD-L1, genetic variation, serum sPD-L1) utilizing newly obtained or archival tumor tissue and blood, including serum and plasma.

5) **Objective**: To evaluate the progression free survival by investigator review in the next line of therapy (PFS2) in subjects treated with pembrolizumab compared to standard treatment.

4.0 BACKGROUND & RATIONALE

4.1 Background

Pembrolizumab is a potent humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) with high specificity of binding to the programmed cell death 1 (PD-1) receptor, thus inhibiting its interaction with programmed cell death ligand 1 (PD-L1) and programmed cell death ligand 2 (PD-L2). Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an intravenous (IV) immunotherapy for advanced malignancies. Keytruda™ (pembrolizumab) is indicated for the treatment of patients across a number of indications.

Refer to the Investigator's Brochure (IB)/approved labeling for detailed background information on MK-3475.

4.1.1 Pharmaceutical and Therapeutic Background

Pembrolizumab (MK-3475, previously known as SCH 9000475) 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.

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 [1; 14; 18; 19; 20]. 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 [14]. Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. PD-1 has been suggested to regulate tumor-specific T-cell expansion in subjects with melanoma (MEL) [21]. This suggests that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention.

4.1.2 Pre-clinical Studies

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 IB).

4.1.3 Ongoing Clinical Trials

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

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 of this cohort were reported at Annual Meeting of the American Society of Clinical Oncology (ASCO) in 2014 [28], 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).

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%), pruritis (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%); pruritis (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%). There were no pembrolizumab reported grade 5 DR AEs [28]. Preliminary PD-L1 biomarker data from KEYNOTE 012 suggests that the response rate may be enhanced for patients with PD-L1 IHC expression. Using a Youden-Index derived PD-L1 IHC cutpoint of 50% tumor proportion score (TPS), the response rate (RR) in patients with high PD-L1 expression was 45.5%, compared to 11.4% 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 will plan to evaluate PD-L1 expression using a 1% CPS cut-off in addition to the 50% TPS previously specified. We will continue the stratification of randomization according to the 50% TPS cut-off as already ongoing, and will plan to

correlate PD-L1 expression with clinical outcome according to both IHC criteria. All analysis of PD-L1 testing was based solely on the KEYNOTE 012 clinical trial as we remain blinded to the ongoing KEYNOTE 040 database. Additionally, subject-level PD-L1 biomarker results will continue to be masked in the database to the study team at the Sponsor including clinical, statistical, statistical programming, and data management personnel until the time of the planned efficacy analysis(es).

4.1.4 Information on Other Trial-Related Therapy

The proposed choice of single agent methotrexate, single agent docetaxel, or single agent cetuximab as the standard of care control arm is based on currently approved products in head and neck cancer, common usage in the second line setting, input from key opinion leaders, and prior precedence in 2nd line (2L) registration trials.

Methotrexate has a registered indication for usage as a single agent in the treatment of epidermoid cancers of the head and neck. It has been the most common comparator standard historically for recurrent/metastatic head and neck cancer. For example, randomized studies evaluating gefitinib [29], edatrexate [30], and platin-based doublet chemotherapy [31] in recurrent/metastatic head and neck cancer have all utilized methotrexate as the comparator arm. Contemporary studies including the recently completed phase III trial of afatinib in recurrent/metastatic head and neck cancer continue to use methotrexate as the comparator. However, its usage in the head and neck cancer community outside of a clinical trial is more limited, so other standard of care options are provided for this trial.

Docetaxel has a registered indication in squamous cell carcinoma of the head/neck for locally advanced disease in combination with cisplatin and 5-fluorouracil. However, it is commonly given in the recurrent/metastatic setting as a single agent with response rates (RR) ranging from 6-42%, depending on the line of therapy and patient population. For example, significant clinical activity of weekly docetaxel in a phase II study of 38 subjects was seen with a response rate of 42% in the 1L (1st line) recurrent/metastatic setting [32]. In addition, a randomized phase II study of weekly docetaxel vs. methotrexate showed a higher response rate for docetaxel (27%) in the 1L recurrent/metastatic setting, although survival rates were comparable [33]. Phase III studies using weekly docetaxel as the control arm in the 1L/2L setting have also been performed, confirming the activity of docetaxel in the predominantly 2L setting, although RRs were more modest at 6.2% [34]. Thus single agent docetaxel on a weekly schedule has been shown to have activity in recurrent/metastatic disease, and is utilized particularly in head and neck cancer subjects who have not been previously exposed to taxanes.

Cetuximab has a registered indication for the treatment of recurrent or metastatic squamous cell carcinoma of the head and neck progressing after platinum-based therapy. In an open-label phase II study of 103 recurrent/metastatic head and neck cancer subjects treated with single agent cetuximab after failing to respond to platinum-based therapy, the response rate was 13% [35]. The activity of single agent cetuximab in recurrent/metastatic disease has also been seen in other studies, with response rates of 8-11% [36].

Therefore, these 3 agents will be used as standard treatment options in the comparator arm of this study. This allows the investigator to select from 3 options for subjects randomized to the standard therapy arm. When choosing a standard therapy, the investigator should refer to

the Summary of Product Characteristics (with special consideration for any contraindications, special warnings and precautions of use), and/or according to local guidelines.

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

Head and neck cancer describes a range of tumors that arise in the head and neck region, which includes the oral cavity, pharynx, larynx, nasal cavity, paranasal sinuses, thyroid, and salivary glands. The worldwide incidence of head and neck cancer exceeds half a million cases annually, ranking it as the fifth most common cancer worldwide [37]. And although the head and neck region contains a wide diversity of structures and cell types, the vast majorities of head and neck cancers arise from the mucosa of the upper aerodigestive tract and are predominantly squamous cell in origin.

Subjects with locally recurrent and metastatic head and neck cancer present a therapeutic challenge. And although both conventional cytotoxic drugs and molecularly targeted compounds have activity in metastatic and recurrent head and neck cancer, the prognosis of subjects with recurrent or metastatic head and neck squamous cell cancer is generally poor despite these therapies. The median survival in most series is 6-9 months with limited treatment options and substantial morbidity. Single agent therapy and combination regimens using either conventional cytotoxic chemotherapy and/or molecularly targeted agents, combined with best supportive care is palliative for subjects with recurrent head and neck cancer. The most widely used agents include platinum compounds (cisplatin, carboplatin), taxanes (docetaxel, paclitaxel), methotrexate, 5-fluorouracil, and cetuximab.

After failure of first-line chemotherapy in the recurrent/metastatic setting, objective responses to second-line cytotoxic chemotherapy are uncommon, particularly when contemporary response criteria are applied. 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 subjects, with a median overall survival of 6.7 months [29]. Other single agents have produced higher response rates but this has generally been associated with increased toxicity, and without an impact on survival.

In this trial, subjects with oropharynx cancer will be stratified by HPV status (positive or negative). The favorable prognostic significance of HPV-positive head and neck cancers in the oropharynx has been increasingly established [38]. Preliminary data of single agent pembrolizumab in head and neck cancer patients in KEYNOTE 012 demonstrate efficacy in both HPV positive and HPV negative patients. Site or central assessment of HPV using immunohistochemistry (IHC) staining for the p16 protein will be used for this population prior to randomization.

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

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

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 2 mg/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 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 patients, Q3W dosing will be further studied.

The rationale for further exploration of 2 mg/kg and comparable doses of pembrolizumab in solid tumors is based on: 1) similar efficacy and safety of pembrolizumab when dosed at either 2 mg/kg or 10 mg/kg Q3W in melanoma patients, 2) the flat exposure-response relationships of pembrolizumab 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 pembrolizumab (as assessed by the population PK model) and 4) the assumption that the dynamics of pembrolizumab 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 pembrolizumab 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

4.2.3.1.1 Primary

Overall survival (OS) is the gold standard endpoint to demonstrate superiority of antineoplastic therapy. Progression free survival (PFS) may be considered an acceptable scientific endpoint for a randomized phase III trial to demonstrate superiority of a new antineoplastic therapy as a number of ongoing randomized trials in recurrent/metastatic head and neck cancer have used PFS as a primary endpoint. RECIST 1.1 will be used to determine the dates of progression as this methodology is accepted by regulatory authorities (see Section 12.7). Because the treatment assignment is unblinded, images will be read by independent central radiologists blinded to treatment assignment to minimize bias in the response assessments. In addition, radiologic progression will be based on the central assessment of progression, rather than site assessment. Expedited verification of radiologic progression as determined by central review (following site assessment of progression) will be communicated to the site.

Figure 3 shows the process for tumor assessment by site and central imaging vendor.

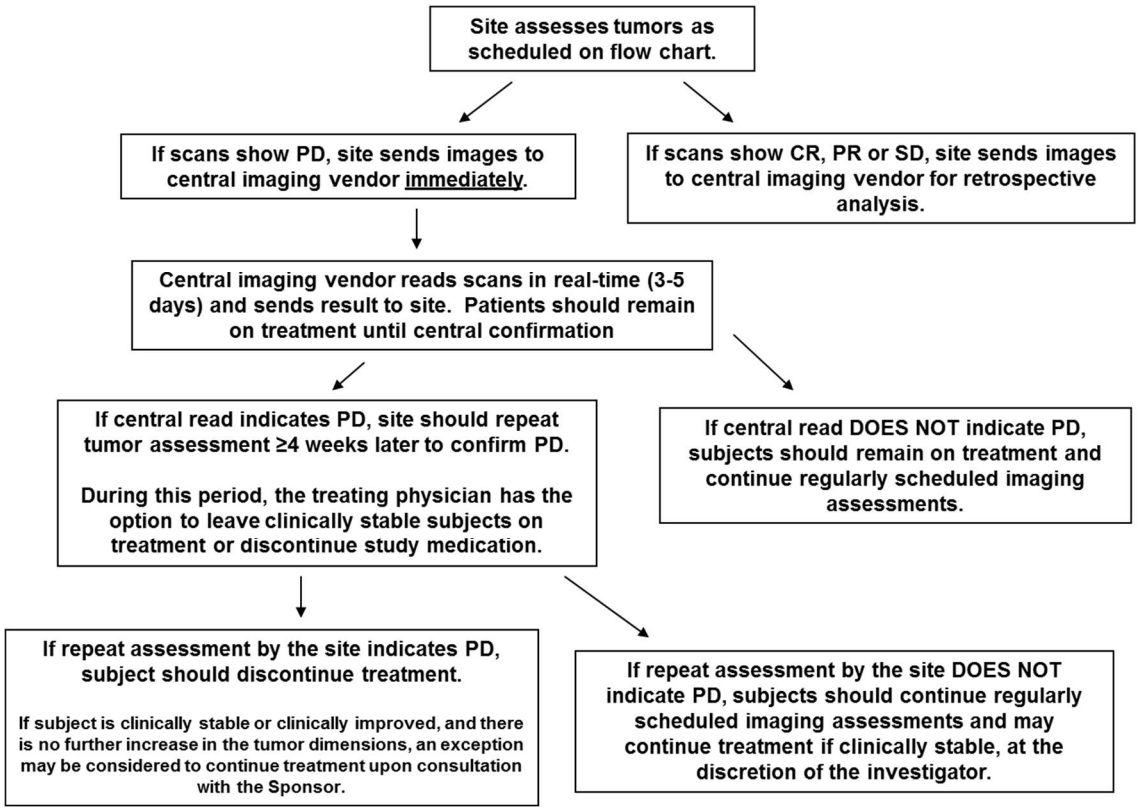

Figure 3 Imaging Process

Note: See Site Imaging Manual regarding timing for submission of verification of progression scans and for all other study imaging.

4.2.3.2 Modified RECIST

RECIST 1.1 will be adapted to account for the unique tumor response characteristics seen with treatment of MK-3475. Immunotherapeutic agents such as 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 a clinical response after an initial increase in tumor burden or even the appearance of new lesions. Standard RECIST may not provide an accurate response assessment of immunotherapeutic agents such as MK-3475. Therefore, RECIST 1.1 will be used with the following adaptations:

If independent central assessment (following initial site-assessed PD) verifies PD, tumor assessment should be repeated by the site ≥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 demonstrates ≥ 20% increase in tumor burden compared to nadir and an absolute increase in 5mm, PD is confirmed and subjects will be discontinued from study therapy (exception noted in section 7.1.2.6.3). For additional scenarios regarding

new lesions and non-target disease, see Procedures Manual. NOTE: If a subject has 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.

In determining whether or not the tumor burden has increased or decreased, investigators should consider all target lesions as well as non-target lesions (please refer to the Imaging section of the Procedures Manual).

In subjects who have a verification of radiological PD by central imaging vendor (following site-assessed PD), it is at the discretion of the treating physician whether to continue a subject on study treatment until repeat imaging is obtained. This clinical judgment decision should be based on the subject's overall clinical condition, including performance status, clinical symptoms, and laboratory data. Subjects may receive MK-3475 or standard treatment (control arm) 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

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.

It must be emphasized that subjects remain on treatment if clinically stable until RECIST 1.1 defined progression is verified by blinded independent central radiology for both the experimental and control arms of the study, and that the schedule of assessments be adhered to. If study therapy is discontinued for toxicity but the subject is otherwise stable, the subject should continue radiologic assessments as indicated in the flow chart until RECIST 1.1 defined progression has been established or the subject starts a new anti-cancer therapy.

4.2.3.3 Patient Reported Outcomes

The EORTC QLQ-C30, EORTC QLQ-H&N35, EQ-5D and Health Economic Assessment are not pure efficacy or safety endpoints because they are affected by both disease progression and treatment tolerability.

4.2.3.3.1 eEORTC QLQ-C30 and eEORTC QLQ-H&N35

The EORTC-QLQC30 is the most widely used cancer specific HRQoL instrument, which contains 30 items and measures five functional dimensions (physical, role, emotional,

cognitive and social), three symptom items (fatigue, nausea/vomiting, and pain), six single items (dyspnea, sleep disturbance, appetite loss, constipation, diarrhea, and financial impact), and a global health and quality of life scale [39].

The EORTC QLQ-H&N35 is in use worldwide as one of the standard instruments for measuring quality of life in head and neck cancer subjects [40, 41] and consists of 7 multi-item scales measuring pain in the mouth, problems with swallowing, senses, speech, social eating and social contact, and 11 single-item scales assessing problems with teeth, mouth opening, dry mouth, sticky saliva, coughing, feeling ill, use of analgesics, use of nutritional supplements, use of feeding tube, weight gain, and weight loss [42]. The EORTC QLQ-C30 and EORTC QLQ-H&N35 are psychometrically and clinically validated instruments appropriate for assessing quality of life in subjects with head and neck cancer. These instruments were used in the EXTREME registration trial comparing platin-5-fluorouracil alone versus combined with cetuximab as first-line treatment in recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN), which led to the FDA approval of cetuximab monotherapy in subjects with recurrent or metastatic SCCHN refractory to cisplatin [43, 44]. They were also used in the phase III trial of subjects with locoregionally advanced head and neck cancer receiving radiotherapy alone with radiotherapy plus cetuximab [45].

The EORTC QLQ-C30 and EORTC QLQ-H&N35 are to be completed at various time points as specified in the study Flow Chart, beginning with Cycle 1 until 30 days post-treatment discontinuation.

4.2.3.3.2 eEuroQuol EQ-5D

The eEuroQol-5D (eEQ-5D) is a standardized instrument for use as a measure of health outcome. The eEQ-5D will provide data for use in economic models and analyses including developing health utilities or QALYs. The five health state dimensions in this instrument include the following: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression (5). Each dimension is rated on a three point scale from 1 (extreme problem) to 3 (no problem). The eEQ-5D also includes a graded (0 to 100) vertical visual analog scale on which the subject rates his or her general state of health at the time of the assessment. The eEQ-5D will always be completed by subjects first before completing the eEORTC QLQ C-30 and EORTC QLQ-H&N35 and is to be completed at various time points as specified in the Trial Flow Chart, beginning with Cycle 1 until 30 days post-treatment discontinuation.

4.2.3.3.3 Health Economic Assessment

The Health Economic Assessment (HEA) form will be completed via an interview with the subject by qualified site personnel. The objective of the HEA is for the site personnel to collect information from subjects on all the non-study related health care contacts made throughout the trial. The HEA is to be completed at various time points as specified in the Trial Flow Chart, beginning with Cycle 2 until 30 days post-treatment discontinuation.

4.2.3.4 Planned Exploratory Biomarker Research

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

Assays may include but are not be limited to:

Immunohistochemistry (IHC)

PD-L1 expression in tumor tissue will be characterized by commercial grade IHC assay to explore the relationship between tumor PD-L1 expression and response to treatment with pembrolizumab. Heterogeneous PD-L2 expression has been demonstrated on tumor cells as well as stromal cells and associated endothelium that may have independent predictive value from PD-L1 expression in head and neck cancer. Pilot analysis of PD-L2 expression by a lab-developed IHC assay tested in the KEYNOTE 012 B and B2 HNSCC cohorts suggest that PD-L2 expression may independently predict clinical benefit of pembrolizumab in tumors absent for PD-L1 expression [46]. Therefore, other biomarkers contributing to the PD-1/PD-L1 axis, including testing for PD-L2 may also be explored.

Transcriptional Analyses

Messenger RNA (mRNA) expression profiling in archival material will be completed to assess expression of approximately 700 genes and further evaluate gene expression signatures found to be statistically significantly associated with clinical response to pembrolizumab in KEYNOTE 012 B [47] and have also been confirmed independently in the B2 HNSCC cohorts to show highly statistically significant associations. These signatures contain genes believed to capture a key inflammatory phenotype of an ongoing adaptive immune response including IFNγ signaling, cytolytic activity, antigen presentation and T-cell trafficking, as well as inhibitory mechanisms that are evident in T-cell homeostasis. The hypothesis to be tested in this trial is that pembrolizumab induces responses in tumors that reflect an inflamed/immune phenotype as captured by such gene expression signatures. Global profiling will also be pursued. Expression of individual genes of interest related to the immune system may also be evaluated. MicroRNA profiling may also be pursued in serum samples.

Proteomic analysis

In addition to expression on the tumor tissue, PD-L1 can be shed from tumor and released into the blood. Enzyme-linked immunoassay can measure PD-L1 in serum and correlate this expression with response to pembrolizumab therapy, as well as levels of PD-L1 IHC or protein in the tumor. Blood would be a less invasive compartment compared to tumor from which to measure PD-L1 protein biomarker. In addition to this specific protein biomarker, both tissue and blood derivatives can be subjected to proteomic profiling studies using a variety of platforms that could include but are not limited to immunoassay, liquid

chromatography/mass spectrometry. This approach could identify novel protein biomarkers that could aid in patient selection for pembrolizumab therapy.

Gene Analyses

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

4.2.3.5 Future Biomedical Research

The Sponsor will conduct Future Biomedical Research on specimens routinely and specifically collected 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.

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

Male/Female subjects with recurrent or metastatic (R/M) head and neck squamous cell carcinoma (HNSCC) of at least 18 years of age will be enrolled in this trial. Note: When selecting a standard treatment regimen prior to randomization, investigators should consider contraindications, special warnings, and precautions of use that are specific for the treatment.

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 documented informed consent for the trial. The subject may also provide consent for Future Biomedical Research. However, the subject may participate in the main trial without participating in Future Biomedical Research.
2. Be ≥ 18 years of age on the day of providing documented informed consent.
3. Have histologically or cytologically-confirmed recurrent (recurrent disease that is not amenable to curative treatment with local and/or systemic therapies) or metastatic (disseminated) head and neck squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, and larynx that is considered incurable by local therapies. Subjects may not have any other primary tumor site (e.g. nasopharynx).
4. Prior platinum failure as defined by, either:

    a. Disease progression after treatment with a platinum-containing regimen for recurrent (disease not amenable to curative treatment)/metastatic disease

    Note: Disease progression may occur at any time during or after a platinum-containing regimen (e.g. carboplatin or cisplatin) which was administered in either 1L or 2L in the recurrent/metastatic setting.

    OR

    b. Recurrence/progression within 6 months of prior multimodal therapy using platinum (e.g. locally advanced setting)

5. Have results from local testing of HPV positivity for oropharyngeal cancer defined as p16 IHC testing using the CINtec® assay and a 70% cutoff point. Please see Section 7.1.2.7 for details. If HPV status has previously been tested using this procedure, no retesting is required.

    Note: HPV stratification in this trial will be performed using local or central testing of HPV status in patients with oropharynx cancer. Oral cavity, hypopharynx, and larynx cancer are not required to undergo HPV testing by p16 IHC as by convention they are assumed to be HPV negative.

6. Have provided tissue for PD-L1 biomarker analysis – and received the PD-L1 results – (PD-L1 analysis will be blinded to both site and sponsor) from a newly obtained core or excisional biopsy. (Tissue beyond the 42-day window and up to 6 months may be considered with Sponsor consultation as long as no intervening systemic regimen has been taken.) Repeat samples may be required if adequate tissue is not provided.

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

   Note: If emerging data indicate a high concordance in PD-L1 expression scores between newly obtained and archival samples, archived samples may be acceptable.

7. Have radiographically measurable disease based on RECIST 1.1 as determined by the site. Tumor lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions.
8. Have a performance status of 0 or 1 on the ECOG Performance Scale, as assessed within 10 days of treatment initiation.
9. Demonstrate adequate organ function as defined in Table 1, all screening labs should be performed within 10 days of treatment initiation.

Table 1 Adequate Organ Function Laboratory Values

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

10. Female subjects of childbearing potential should have a negative serum pregnancy test within 72 hours prior to receiving the first dose of study medication. A urine test can be considered if a serum test is not appropriate.

11. 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 pembrolizumab (Reference Section 5.7.2) or through 120-180 days after the last dose of docetaxel, methotrexate or cetuximab, according to local standard of care. Subjects of childbearing potential are those who have not been surgically sterilized or have not been free from menses for > 1 year.

    Note: For UK subjects: 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 (and specifically through 180 days after the last dose of docetaxel or methotrexate) (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.

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

12. 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 pembrolizumab or through 120-180 days after the last dose of docetaxel, methotrexate or cetuximab, according to local standard of care.

    Note: For France subjects: 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 (and specifically through 180 days after the last dose of docetaxel).

    Note: For UK subjects: 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 (and specifically through 180 days after the last dose of docetaxel or methotrexate).

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

5.1.3 Subject Exclusion Criteria

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

1. Has disease that is suitable for local therapy administered with curative intent.
2. Had progressive disease within three months of completion of curatively intended treatment for locoregionally advanced or recurrent HNSCC.

   Note: This exclusion criterion is only applicable for subjects who have not had treatment in the metastatic/recurrent setting.

3. Is currently participating in and receiving study therapy or has participated in a study of an investigational agent and received study therapy or used an investigational device within 4 weeks prior to randomization.

   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.

4. Was previously treated with 3 or more systemic regimens given for recurrent and/or metastatic disease.
5. Patients previously treated in the recurrent/metastatic setting or resistant in the locally advanced setting to one of the 3 standard of care agents in this trial (i.e. docetaxel, methotrexate, or cetuximab) may not receive the same agent if randomized to the standard treatment arm (see Section 5.2 for details).
6. 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.

7. 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.
8. 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.
9. Has a diagnosed and/or treated additional malignancy within 5 years prior to randomization with the exception of curatively treated basal cell carcinoma of the skin, squamous cell carcinoma of the skin and/or curatively resected *in situ* cervical and/or breast cancers.
10. 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.
11. Has active autoimmune disease that has required systemic treatment in past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (eg., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is permitted.
12. Has active, non-infectious pneumonitis.
13. Has an active infection requiring systemic therapy.
14. 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.
15. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.
16. 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.

17. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent or has previously participated in Merck MK-3475 clinical trials.

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

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

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

5.2 Trial Treatment(s)

The treatments to be used in this trial are outlined below in .

Table 2 Trial Treatments

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period	Use
Pembrolizumab	200 mg	Q3W	IV infusion	Day 1 of each cycle (3 week cycles)	Experimental
Methotrexate*	40 mg/m^2 (may be increased to a maximum of 60 mg/m^2 weekly in the absence of toxicity – see Section 5.2.2.2)	QW	IV infusion	Days 1, 8, and 15 of each cycle (3 week cycles)	Active-comparator
Docetaxel	75 mg/m^2	Q3W	IV infusion	Day 1 of each cycle (3 week cycles)	Active-comparator
Cetuximab	400 mg/m^2 loading dose followed by 250mg/m^2	QW	IV infusion	Days 1, 8 and 15 of each cycle (3 week cycles)	Active-comparator
*Methotrexate exits slowly from third space compartment (e.g. pleural effusions or ascites). This results in a prolonged terminal plasma half-life and the potential for unexpected toxicities. In patients with significant third space accumulations, it is advisable to evacuate the fluid before treatment.					

Note: Patients resistant to one of the 3 standard of care agents in this trial (i.e. docetaxel, methotrexate, or cetuximab) may not receive the same agent if randomized to the standard treatment arm.

Prior resistance or failure to the standard of care agent is defined by:

- Recurrence or progression of disease within 6 months of prior multimodal therapy using SOC agent (e.g. locally advanced setting)

- Previously received a SOC containing regimen for recurrent/metastatic disease

Trial treatment should be given on the day of randomization, but up to 3 days after randomization is permitted.

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

5.2.1 Dose Selection/Modification

5.2.1.1 Dose Selection (Preparation)

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

Treatment on the standard treatment arm will be prepared and administered as per the approved product label. The body surface area (BSA) in m^2 should be calculated per local guidance.

5.2.1.2 Dose Modification (Escalation/Titration/Other)

5.2.1.2.1 Immune-Related Events and Dose Modification (Withhold, Treat, Discontinue)

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

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

Dose Modification and Toxicity Management Guidelines for irAEs associated with pembrolizumab monotherapy, coformulations, or IO combinations are provided in Table 3. Hematological Toxicity Management Guidelines for Pembrolizumab are provided in Table 4.

Table 3 Dose Modification and Toxicity Management Guidelines for Immune-related Adverse Events Associated with Pembrolizumab Monotherapy, Coformulations or IO Combinations

General instructions:

1. Severe and life-threatening irAEs should be treated with IV corticosteroids followed by oral steroids. Other immunosuppressive treatment should begin if the irAEs are not controlled by corticosteroids.
2. Pembrolizumab monotherapy, coformulations or IO combinations must be permanently discontinued if the irAE does not resolve or the corticosteroid dose is not ≤10 mg/day within 12 weeks of the last treatment.
3. The corticosteroid taper should begin when the irAE is ≤ Grade 1 and continue at least 4 weeks.
4. If pembrolizumab monotherapy, coformulations or IO combinations have been withheld, treatment may resume after the irAE decreased to ≤ Grade 1 after corticosteroid taper.

irAEs	Toxicity Grade (CTCAEv4.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment • Add prophylactic antibiotics for opportunistic infections
	Recurrent Grade 2 or Grade 3 or 4	Permanently discontinue		

irAEs	Toxicity Grade (CTCAEv4.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Diarrhea / Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus) • Participants with ≥Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

irAEs	Toxicity Grade (CTCAEv4.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring 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	
T1DM or Hyperglycemia	New onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold a	• Initiate insulin replacement therapy for participants with T1DM • Administer anti-hyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes

irAEs	Toxicity Grade (CTCAEv4.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
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 a		
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 a		
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		

irAEs	Toxicity Grade (CTCAEv4.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Myocarditis	Grade 1	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 2, 3 or 4	Permanently discontinue		
All Other irAEs	Persistent Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 3	Withhold or discontinue b		
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

AE(s)=adverse event(s); ALT= alanine aminotransferase; AST=aspartate aminotransferase; CTCAE=Common Terminology Criteria for Adverse Events; DRESS=Drug Rash with Eosinophilia and Systemic Symptom; GI=gastrointestinal; IO=immuno-oncology; ir=immune related; IV=intravenous; SJS=Stevens-Johnson Syndrome; T1DM=type 1 diabetes mellitus; TEN=Toxic Epidermal Necrolysis; ULN=upper limit of normal.

Note: Non-irAE will be managed as appropriate, following clinical practice recommendations.

a The decision to withhold or permanently discontinue pembrolizumab monotherapy, coformulations or IO combinations is at the discretion of the investigator or treating physician. If control achieved or ≤ Grade 2, pembrolizumab monotherapy, coformulations or IO combinations may be resumed.

b Events that require discontinuation include, but are not limited to: Guillain-Barre Syndrome, encephalitis, myelitis, DRESS, SJS, TEN and other clinically important irAEs (eg, vasculitis and sclerosing cholangitis).

Table 4 Hematological Toxicity Management Guidelines for Pembrolizumab

Toxicity	Grade	Hold Treatment	Discontinue Subject
Hematological	Any Gr 2 and Gr 3 neutropenia, thrombocyto-penia and anemia	Neutrophils recover to > 1000 cells/mm3 Platelets recover to > 75,000 cells/mm3 Anemia resolves to Grade 1 or baseline	N/A
	3 All other AEs other than Gr 3 neutropenia, thrombocyto-penia and anemia	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Neutrophils recover to > 1000 cells/mm3 Platelets recover to > 75,000 cells/mm3 Anemia resolves to Grade 1 or baseline Toxicity resolves to Grade 0-1	

Dosing interruptions are permitted in the case of medical/surgical events or logistical reasons not related to study therapy (e.g., elective surgery, unrelated medical events, patient vacation, and/or holidays). Subjects 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 clinical database (the case report form).

In case toxicity does not resolve to Grade 0-1 within 12 weeks after the last infusion, trial treatment should be discontinued after consultation with the Sponsor. With investigator and Sponsor agreement, subjects with a laboratory adverse event still at Grade 2 after 12 weeks may continue in the trial only if asymptomatic and controlled. Dose interruptions of pembrolizumab for intolerable Grade 2 drug-related adverse events may be considered after consultation with the Sponsor. Patients who experience a 3rd occurrence of the same toxicity requiring dose modification must be discontinued from study medication. For information on the management of adverse events, see Section 5.6.1.

5.2.1.2.2 Dose Modification for Standard Treatment Methotrexate, Docetaxel, or Cetuximab

In general, treatment with methotrexate, docetaxel, or cetuximab will be withheld for drug-related Grade 4 hematologic toxicities and for non-hematologic toxicity ≥ Grade 3 and subsequent doses modified as per Table 5 below. Dose modifications will be applied for all subsequent doses. Specific dose modification guidance for docetaxel and cetuximab is found below in Sections 5.2.1.2.2.1 and 5.2.1.2.2.2. Dose modifications for intolerable Grade 2 drug-related adverse events may be considered after consultation with the Sponsor.

Table 5 Dose Modification Guidelines for Drug-Related Adverse Events on the Standard Treatment Arm

Toxicity	Grade	Occurrence	Hold Treatment	Dose Modification	Treatment Discontinuation
Neutropenia±	Grade 2, 3	All	Hold treatment until neutrophils recover to > 1000 cells/mm3 OR to >1500 cells/mm3 for UK and France+	N/A	N/A
	Grade 4	1st occurrence	Hold treatment until neutrophils recover to > 1000 cells/mm3 OR to >1500 cells/mm3 for UK and France+	Restart treatment at: Methotrexate: Decrease dose by 10 mg/m2* Docetaxel: 60 mg/m2 Cetuximab: 200 mg/m2	Toxicity does not resolve within 12 weeks of last infusion Permanent discontinuation should be considered for any severe or life-threatening event
		2nd occurrence	Hold treatment until neutrophils recover to > 1000 cells/mm3 OR to >1500 cells/mm3 for UK and France+	Restart treatment at: Methotrexate: Decrease dose by an additional 10 mg/m2* Docetaxel: 45 mg/m2 Cetuximab: 150 mg/m2	
		3rd occurrence	Yes	N/A	Yes

Toxicity	Grade	Occurrence	Hold Treatment	Dose Modification	Treatment Discontinuation
Thrombocytopenia	Grade 2, 3	All	Hold treatment until platelets recover to > 75,000 cells/mm3	N/A	N/A
	Grade 4	1st occurrence	Hold treatment until platelets recover to > 75,000 cells/mm3	Restart treatment at: Methotrexate: Decrease dose by 10 mg/m2* Docetaxel: 60 mg/m2 Cetuximab: 200 mg/m2	Toxicity does not resolve within 12 weeks of last infusion Permanent discontinuation should be considered for any severe or life-threatening event
		2nd occurrence	Hold treatment until platelets recover to > 75,000 cells/mm3	Restart treatment at: Methotrexate: Decrease dose by an additional 10 mg/m2* Docetaxel: 45 mg/m2 Cetuximab: 150 mg/m2	
		3rd occurrence	Yes	N/A	Yes

Toxicity	Grade	Occurrence	Hold Treatment	Dose Modification	Treatment Discontinuation
Anemia	Grade 2, 3	All	Until anemia resolves to Grade 1 or baseline	N/A	N/A
	Grade 4	1st occurrence	Until anemia resolves to Grade 1 or baseline	Restart treatment at: Methotrexate: Decrease dose by 10 mg/m2* Docetaxel: 60 mg/m2 Cetuximab: 200 mg/m2	Toxicity does not resolve within 12 weeks of last infusion Permanent discontinuation should be considered for any severe or life-threatening event
		2nd occurrence	Until anemia resolves to Grade 1 or baseline	Restart treatment at: Methotrexate: Decrease dose by an additional 10 mg/m2* Docetaxel: 45 mg/m2 Cetuximab: 150 mg/m2	
		3rd occurrence	Yes	N/A	Yes

Toxicity	Grade	Occurrence	Hold Treatment	Dose Modification	Treatment Discontinuation
Non-hematological toxicity and other hematological toxicity not described above Exceptions for subjects receiving docetaxel and cetuximab noted in Section 5.2.1.2.2.1 and 5.2.1.2.2.2 below.	Grade 1, 2	All	No	None	N/A
	Grade 3, 4	1st occurrence	Yes, until toxicity resolves to Grade 0-1 or baseline	Restart treatment at**: Methotrexate: Decrease dose by 10 mg/m2* Docetaxel: 60 mg/m2 Cetuximab: 200 mg/m2	Toxicity does not resolve within 12 weeks of last infusion Permanent discontinuation should be considered for any severe or life-threatening event
		2nd occurrence	Yes, until toxicity resolves to Grade 0-1 or baseline	Restart treatment at: Methotrexate: Decrease dose by an additional 10 mg/m2* Docetaxel: 45 mg/m2 Cetuximab: 150 mg/m2	
		3rd occurrence	Yes	N/A	Yes

± Docetaxel is contraindicated in subjects with neutrophil level <1500 mm3.
+ As per the Health Authority requests for these specific countries.
* For subjects receiving methotrexate at higher doses than 40 mg/m2, additional dose modifications may occur after consultation with the Sponsor
** Dose reduction is at physician discretion for grade 3 lab abnormalities without clinical significance

In cases where the toxicity does not resolve to Grade 0-1 within 12 weeks after the last infusion, trial treatment should be discontinued after consultation with the Sponsor. With investigator and Sponsor agreement, subjects with a laboratory adverse event still at Grade 2 after 12 weeks may continue in the trial only if asymptomatic and controlled. For information on the management of adverse events, see Section 5.6.1.

5.2.1.2.2.1 Specific Dose Modifications for Docetaxel

Docetaxel should not be given to subjects with bilirubin > ULN, or to subjects with AST and/or ALT > 1.5 x ULN with concomitant alkaline phosphatase (AP) >2.5 x ULN as subjects with laboratory values above these limits are at increased risk of serious adverse events [refer to local product label].

Note: For UK subjects: subjects with impaired vision, representing a new change from baseline while on treatment (ophthalmic events ≥Grade 2), should have docetaxel treatment held and be referred promptly for an ophthalmology consultation.+

Dose modifications for subjects receiving docetaxel are detailed below in Table 6.

Table 6 Docetaxel Dose Modification for Drug-Related Adverse Events

Toxicity	Grade	Occurrence	Hold Treatment	Dose Modification	Treatment Discontinuation
Liver dysfunction	AST/ALT >2.5 to ≤5 × ULN and AP ≤2.5 × ULN, or AST/ALT >1.5 to ≤5 × ULN and AP >2.5 to ≤5 × ULN		Yes	Restart treatment at 60 mg/m2	N/A
	AST/ALT >5 × ULN and/or AP >5 × ULN		Yes	N/A	Discontinue upon onset
Peripheral Neuropathy	Grade 3, 4		Yes	N/A	Discontinue upon onset
Ophthalmic adverse events+	≥Grade 2		UK subjects: Yes and refer for ophthalmology consultation	N/A	Consult the Sponsor
Oral Mucositis	Grade 3, 4	1st occurrence	Hold until resolved	60 mg/m2	Treatment discontinuation should be considered
	Grade 3, 4	2nd occurrence	Hold until resolved	45 mg/m2	Treatment discontinuation should be considered
		3rd occurrence	Yes	N/A	Yes

+ As per specific UK Health Authority request.

5.2.1.2.2.2 Specific Dose Modifications for Methotrexate

Renal Impairment

For Sweden subjects: subjects with renal impairment enrolled in the study and receiving methotrexate may need close monitoring and/or dose reduction.±

±As per specific Swedish Health Authority request.

Colitis or Peptic Ulcer

For UK subjects: subjects with ≥grade 2 colitis or peptic ulcer symptoms should discontinue methotrexate treatment.+

+ As per specific UK Health Authority request.

5.2.1.2.2.3 Specific Dose Modifications for Cetuximab

Infusion Reactions

Subjects who experience Grade 1, 2 or non-serious Grade 3 infusion reactions should have the infusion rate permanently reduced by 50% and continue to receive antihistamine premedication prior to administration. Cetuximab should be discontinued immediately for serious infusion reactions that require medical intervention and/or hospitalization. Subjects who experience serious infusion reactions will be discontinued from the study.

Dermatologic Toxicity

The dosing of cetuximab will be delayed 1 to 2 weeks in the case of severe (Grade 3 or 4) acneiform rash. Cetuximab should be discontinued for a grade 4 acneiform rash which has not improved after a 2 week delay in treatment. However treatment may be delayed up to 12 weeks for grade 3 acneiform rash for recovery. If dermatologic toxicity improves after the delay then the dose of cetuximab will be reduced as indicated in Table 7. If dermatologic toxicity does not improve after the delay cetuximab will be discontinued.

Keratitis

UK subjects who experience ≥Grade 2 keratitis, representing a new change from baseline while on treatment, should have cetuximab treatment held and be referred promptly for an ophthalmology consultation, as indicated in Table 7.

Table 7 Cetuximab Dose Modification for Rash and Keratitis

Severe Acneiform Rash (≥ Grade 3)	Dose Interruption	Outcome	Dose Modification
1st occurrence	Delay treatment: Grade 3 up to 12 weeks Grade 4 up to 2 weeks	Improved	None, continue at 250 mg/m2
2nd occurrence	Delay treatment: Grade 3 up to 12 weeks Grade 4 up to 2 weeks	Improved	Permanently reduce dose to 200 mg/m2
3rd occurrence	Delay treatment: Grade 3 up to 12 weeks Grade 4 up to 2 weeks	Improved	Permanently reduce dose to 150 mg/m2
4th occurrence	Discontinue	N/A	N/A
Keratitis (≥ Grade 2)+	UK subjects: Hold treatment and refer for ophthalmology consult	N/A	Consult the Sponsor

+ As per specific UK Health Authority request.

5.2.2 Timing of Dose Administration

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

Trial treatment of methotrexate, docetaxel, or cetuximab may be administered up to 3 days before or after the scheduled dosing date for administrative reasons per the investigator's judgment (up to 3 days after randomization is permitted).

Note: 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. The reason for interruption should be documented in the patient's study record.

All trial treatments will be administered on an outpatient basis.

5.2.2.1 Pembrolizumab

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

Pembrolizumab 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 Pharmacy Manual contains specific instructions for the preparation of the pembrolizumab infusion fluid and administration of infusion solution.

5.2.2.2 Methotrexate

Trial treatment of methotrexate should be administered on Days 1, 8 and 15 of each 3 week cycle after all procedures/assessments have been completed as detailed on the Trial Flow Chart (Section 6.0). Methotrexate will be administered as an IV infusion.

All subjects will start treatment at 40 mg/m2. After the first 3 week cycle if there was no hematologic toxicity, no stomatitis, and renal function was normal, the dose may be increased by 10 mg/m2 every 3 week cycle to a maximum of 60 mg/m2 (e.g., in the absence of toxicity, 50 mg/m2 could be given at Cycle 2 and 60 mg/m2 could be given at Cycle 3 and subsequent cycles).

5.2.2.3 Docetaxel

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

Docetaxel 75 mg/m2 will be administered as an IV infusion administered over 1 hour or following local standard of care.

5.2.2.4 Cetuximab

Trial treatment of cetuximab should be administered on Days 1, 8 and 15 of each 3 week cycle after all procedures/assessments have been completed as detailed on the Trial Flow Chart (Section 6.0).

Cetuximab will be given as an initial loading dose on Cycle 1 Day 1 of 400 mg/m2 infused over 120 minutes (maximum infusion rate 10 mg/min) followed by 250 mg/m2 infused over 60 minutes (maximum infusion rate 10 mg/min) for all subsequent doses starting with the Cycle 1 Day 8 administration or following local standard of care.

5.2.3 Trial Blinding/Masking

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

Imaging data for the primary analysis will be centrally reviewed by independent radiologist(s) without knowledge of subject treatment assignment.

The subject-level PD-L1 biomarker results will be masked in the database to the study team at the Sponsor including clinical, statistical, statistical programming, and data management personnel. Access to the PD-L1 subject-level biomarker results will be limited to an unblinded Sponsor clinical scientist, unblinded data management personnel, unblinded Sponsor statistician, and unblinded Sponsor statistical programmer who will be responsible for data review to ensure validity of results and informing the timing of the interim analyses but who will have no other responsibilities associated with the study.

Access to the allocation schedule and the subject-level PD-L1 results for summaries or analyses for presentation to the DMC will be restricted to an unblinded external statistician, and, as needed, an external scientific programmer performing the analysis, who will have no other responsibilities associated with the study.

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

5.3 Randomization or Treatment Allocation

Randomization will occur centrally using an interactive voice response system / integrated web response system (IVRS/IWRS). There are 2 treatment arms. Subjects will be assigned randomly in a 1:1 ratio to pembrolizumab or standard therapy in an unblinded fashion using centrally randomized blocks stratified according to ECOG status, HPV status and PD-L1 status. Randomization will not be stratified by site. The choice of standard therapy for a subject must be identified and documented prior to randomization. Patients randomized to standard therapy who discontinue will not be crossed-over to pembrolizumab.

5.4 Stratification

Randomization will be stratified according to the following factors:

1. Eastern Cooperative Oncology Group (ECOG) Performance Scale (0 vs. 1)
2. HPV status for oropharynx cancer as determined by p16 immunohistochemistry (IHC) tested at a local or central laboratory; HPV status for subjects without oropharynx cancer is considered HPV negative.
3. PD-L1 Status defined by ≥ 50% TPS (Strong Positive vs. Not)

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 from the date of the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered after 30 days after the last dose of trial treatment should be recorded for SAEs and ECIs as defined in Section 7.2.

A short course of steroids may be used as concomitant medication for either treatment of an adverse event or medical condition with Sponsor approval.

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 (with the exception of denosumab)
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab
- Radiation therapy
    - Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be considered for on an exceptional case by case basis after consultation with Sponsor. The subject must have clear measurable disease outside the radiated field. Administration of palliative radiation therapy will be considered clinical progression for the purposes of determining PFS.
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed

virus vaccines and are allowed; however intranasal influenza vaccines (e.g. Flu - Mist®) are live attenuated vaccines, and are not allowed.

- Note: It is acceptable for subjects receiving cetuximab or docetaxel to receive live vaccines while participating in the trial.
- Note: Any licensed COVID-19 vaccine (including for emergency use) in a particular country is allowed in the study as long as they are mRNA vaccines, adenoviral vaccines, or inactivated vaccines. These vaccines will be treated just as any other concomitant therapy.

  Investigational vaccines (i.e., those not licensed or approved for emergency use) are not allowed.

- Glucocorticoids (inhaled steroids as part of a stable regimen for the treatment of asthma/COPD are permitted) 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: For subjects randomized to the standard treatment arm the use of glucocorticoids on trial treatment is acceptable and may be required for premedication.
  - Note: Use of prophylactic corticosteroids to avoid allergic reactions (e.g. IV contrast dye) is permitted.
- Strong inhibitors of the CYP3A4 enzymes (a common list of such agents may be found in Section 12.8) for subjects receiving docetaxel.
  - Note: For subjects randomized to the standard treatment arm that require treatment with a strong inhibitor of CYP3A4, docetaxel may not be chosen as the standard treatment.

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

- In subjects receiving methotrexate, the following treatments should be used minimally: nephrotoxic therapies, NSAIDs, hepatotoxic therapies (including alcohol) and trimethoprim/sulfamethoxazole.

- In subjects receiving cetuximab, contact lens use increases the risk of keratitis.

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

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

5.6 Rescue Medications & Supportive Care

5.6.1 Supportive Care Guidelines for Pembrolizumab

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of 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. (These procedures should be documented in the case report form.)

- Pneumonitis:
    - For Grade 2 events, treat with systemic corticosteroids. When symptoms of Grade 2 events 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 (Grade 3-4 events require permanent discontinuation). 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 of Grade 2 events improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks (Grade 3-4 events require permanent discontinuation).

- 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 liothyroinine, is indicated per standard of care.
  - Grade 3-4 hyperthyroidism
    - Treat with an initial dose of IV corticosteroid followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

Replacement of appropriate hormones may be required as the steroid dose is tapered.

- Hepatic:
  - For Grade 2 events, monitor liver function tests more frequently until returned to baseline values (consider weekly).
    - Treat with IV or oral corticosteroids
  - For Grade 3-4 events, treat with intravenous corticosteroids for 24 to 48 hours.
  - When symptoms of Grade 2 events improve to Grade 1 or less, a steroid taper should be started and continued over no less than 4 weeks (Grade 3-4 events require permanent discontinuation).
- Renal Failure or Nephritis:
  - For Grade 2 events, treat with oral systemic corticosteroids.
  - For Grade 3-4 events, treat with intravenous systemic corticosteroids.
  - When symptoms of Grade 2 events improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks (Grade 3-4 events require permanent discontinuation).
- 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 8 below shows treatment guidelines for subjects who experience an infusion reaction associated with administration of pembrolizumab (MK-3475).

Table 8 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).

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	Stop Infusion. Additional appropriate medical therapy may include but is not limited to: 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.		

5.6.2 Supportive Care Guidelines for Methotrexate

Note: For UK subjects - Subjects with ≥Grade 2 colitis or peptic ulcer symptoms should discontinue methotrexate treatment.

Refer to the approved product label for supportive care guidance.

5.6.3 Supportive Care Guidelines for Docetaxel

Pre-medication(s) for docetaxel will be given as per standard of care. Corticosteroid pre-treatment or post-treatment of docetaxel is acceptable in concordance with the local label or standard of care.

Refer to the approved product label for additional supportive care guidance.

5.6.4 Supportive Care Guidelines for Cetuximab

Subjects receiving cetuximab should be premedicated with an H1 antagonist (e.g., 50 mg of diphenhydramine) intravenously 30-60 minutes prior to the first dose. Premedication for subsequent doses of cetuximab should be given per medical judgment and history of prior infusion reactions.

Guidelines for medical therapy for infusion reactions detailed in Table 8 above are also recommended for reactions due to cetuximab.

Refer to the approved product label for additional supportive care guidance.

5.7 Diet/Activity/Other Considerations

5.7.1 Diet

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

5.7.2 Contraception

Methotrexate has been reported to cause fetal death and/or congenital anomalies [48]. Pembrolizumab, docetaxel and cetuximab may also have adverse effects on a fetus in utero. Furthermore, it is not known if these agents have transient adverse effects on the composition of sperm. Therefore, non-pregnant, non-breast-feeding women may only be enrolled if they are willing to use 2 methods of birth control or are considered highly unlikely to conceive. Highly unlikely to conceive is defined as 1) surgically sterilized, or 2) postmenopausal (a woman who is ≥45 years of age and has not had menses for greater than 1 year will be considered postmenopausal), or 3) not heterosexually active for the duration of the study. The two birth control methods can either be two barrier methods or a barrier method plus a hormonal method to prevent pregnancy. Subjects receiving pembrolizumab should start using birth control from study Visit 1 throughout the study period up to 120 days after the last dose of study therapy. Subjects receiving standard treatment should start using birth control from study Visit 1 throughout the study period up to 120 days - 180 days after the last dose of study therapy (according to local standard of care).

> Note: For UK subjects: 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 (and specifically through 180 days after the last dose of docetaxel or methotrexate).
>
> Note: For France subjects: Male 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 (and specifically through 180 days after the last dose of docetaxel).

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.

For countries or sites that follow the Clinical Trial Facilitation Group (CTFG) guidance, please use the following:

Methotrexate has been reported to cause fetal death and/or congenital anomalies [48]. Pembrolizumab, docetaxel and cetuximab may also have adverse effects on a fetus in utero. Furthermore, it is not known if these agents have transient adverse effects on the composition of sperm. Therefore, non-pregnant, non-breast-feeding women may only be enrolled if they are willing to follow the Clinical Trial Facilitation Group (CTFG) guidance (Final Version 2014-09-15, Sections 4.1 and 4.2) for highly effective birth control as outlined below, or are considered to be 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.

Subjects should use birth control methods that can achieve a failure rate of less than 1% per year when used consistently and correctly and are considered as highly effective birth control methods. Such methods include:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Intravaginal
  - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Injectable
  - Implantable
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomised partner
- Sexual abstinence

Subjects receiving pembrolizumab should start using birth control from study Visit 1 throughout the study period up to 120 days after the last dose of study therapy. Subjects receiving standard treatment should start using birth control from study Visit 1 throughout the study period up to 120 days - 180 days after the last dose of study therapy (according to local standard of care).

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.

Monthly pregnancy testing is recommended per local standards if applicable.

5.7.3 Use in Pregnancy

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

5.7.4 Use in Nursing Women

Methotrexate is excreted into breast milk and its use is contraindicated in nursing women [48]. It is unknown whether pembrolizumab, docetaxel or cetuximab are 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) requests to discontinue treatment
- Radiographic disease progression confirmed by the site at least 28 days after verification of progression by central imaging vendor

  Note: For unconfirmed radiographic disease progression, please see Section 5.8.1
- Unacceptable adverse experiences as described in Section 5.2.1.2
- Intercurrent illness that prevents further administration of treatment
- Investigator's decision to discontinue treatment for 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

  Note: 24 months of study medication is calculated from the date of first dose. Subjects who stop pembrolizumab after 24 months may be eligible for up to 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 will be collected for 90 days after the end of treatment as described in Section 7.2.3.1). Subjects who discontinue for reasons other than progressive disease will have post-treatment follow-up for disease status until disease progression, initiating a non-study cancer treatment, withdrawing consent or becoming lost to follow-up. After documented disease progression each subject will be followed by telephone for overall survival until death, withdrawal of consent, or the end of the study, whichever occurs first.

5.8.1 Treatment after Initial Radiologic Progression

Immunotherapeutic agents such as pembrolizumab may produce antitumor effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with

cytotoxic agents, and can manifest as a clinical response after an initial increase in tumor burden or even the appearance of new lesions.

If independent central assessment verifies initial site assessed PD, tumor assessment may be repeated by the site ≥ 4 weeks later in order to confirm PD with the option of continuing treatment per below while awaiting radiologic confirmation of progression (see Figure 3). 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. In determining whether or not the tumor burden has increased or decreased, investigators should consider all target lesions as well as non-target lesions (please refer to the Procedures Manual).

The decision to continue study treatment after disease progression is verified by the central imaging vendor is at the Investigator's discretion based on the clinical status of the subject as described in Table 9 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 9 Imaging and Treatment After Site-Assessed 1st Radiologic Evidence of PD

	Clinically Stable		**Clinically Unstable**	
	Imaging	**Treatment**	**Imaging**	**Treatment**
Central imaging vendor assessment verifies PD following site-assessed 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

Note: Central imaging assessment should be performed immediately after site-assessed PD to verify PD. Patients should remain on treatment until central imaging assessment is performed.

5.8.2 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 and had at least two treatments with pembrolizumab beyond the date when the initial CR was declared. Subjects who then experience radiographic disease progression may be eligible for up to one year of additional treatment with pembrolizumab at the discretion of the investigator if no cancer treatment was administered since the last dose of pembrolizumab, the subject meets the safety parameters listed in the Inclusion/Exclusion criteria, and the trial is open. Subjects will resume therapy at the same dose and schedule at the time of initial discontinuation. Additional details are provided in Section 7.1.5.2.1. Response or progression in this Second Course Phase will not count towards the ORR and PFS of the primary endpoint in this trial.

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 provides documented informed consent. The overall trial ends when the last subject completes the last trial visit, discontinues from the trial or is lost to follow-up (i.e. the subject is unable to be contacted by the investigator).

Upon study completion, participants are discontinued and may be enrolled in a pembrolizumab extension study.

5.11 Clinical Criteria for Early Trial Termination

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

1. The trial may be stopped early for futility, early benefit or safety at the recommendation of the Data Monitoring Committee (DMC).

6.0 TRIAL FLOW CHART

6.1 Initial Treatment Phase

6.1.1 Pembrolizumab Arm

Trial Period:	Screening Phase		Treatment Cycles (3-Week 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 or per footnote	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			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	X[i]	X[i]	
12-Lead ECG (Local)		X										
Full Physical Examination		X							X			
Directed Physical Examination			X	X	X	X	X	X				
Vital Signs and Weight[k]		X	X	X	X	X	X	X	X			
ECOG Performance Status[n]		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]										

Trial Period:	Screening Phase		Treatment Cycles (3-Week 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 or per footnote	Every 12 weeks
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]		
Urinalysis[o]		X[n]		X		X		X[j]		X[p]		
T3, FT4 and TSH[z]		X[n]		X		X		X[j]		X[p]		
Laboratory Procedures/Assessments: analysis performed by CENTRAL laboratory												
Pharmacokinetics[q]			X[q,r]	X[q]		X[q]				X[q]	X[q]	
Anti-pembrolizumab Antibodies[q]			X[q]	X[q]		X[q]				X[q]	X[q]	
Blood for Genetics[y]			X									
Correlative Blood Samples[s]			X	X	X				X			
Efficacy Measurements												
Tumor Imaging		X[t]				X[u]		X[u]	X[b,v]		X	
Tumor Tissue Collection												
Archival or Newly Obtained Tissue Collection for Subjects with Oropharynx Cancer Tested Locally or Centrally for HPV Status for Stratification (newly obtained may be obtained 42 days prior to treatment initiation)	X[w]											
Newly Obtained Tissue Collection for Biomarker Analysis (Tested Centrally) on All Subjects Prior to Randomization for Stratification (may be obtained 42 days prior to treatment initiation)	X[w]											
Patient Reported Outcomes												
EuroQol EQ-5D			X[x]	X[x]	X[x]	X[j, x]		X[j, x]	X[x]	X[x]		
EORTC QLQ-C30			X[x]	X[x]	X[x]	X[j, x]		X[j, x]	X[x]	X[x]		
EORTC QLQ-H&N 35			X[x]	X[x]	X[x]	X[j, x]		X[j, x]	X[x]	X[x]		

Trial Period:	Screening Phase		Treatment Cycles (3-Week 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 or per footnote	Every 12 weeks
Health Economic Assessment (HEA)				X[x]	X[x]	X[j, x]		X[j, x]	X[x]	X[x]		

a. In general, assessments/procedures are to be performed on Day 1 and prior to the first dose of treatment for each cycle unless otherwise specified. Treatment cycles are 3 weeks. Imaging should be performed at 9 weeks after randomization date and every 6 weeks thereafter (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 by radiologic imaging every 6 weeks (± 7 days) until (1) the start of new anti-cancer treatment, (2) disease progression, (3) death, or (4) the end of the study, whichever occurs first.
c. After the start of new anti-cancer treatment or documented disease progression 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 study. Upon Sponsor notification, all participants who do not/will not have a scheduled study visit or study contact during the Sponsor defined time period will be contacted for their survival status (excluding participants that have a death event previously recorded).
d. In general, the window for each visit is ± 3 days unless otherwise noted. Cycle 1 treatment should be given within 3 days of randomization.
e. Documented consent must be obtained prior to performing any protocol specified procedure. Results of a test performed prior to the subject signing consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame (e.g., within 28 days prior to the first dose of trial treatment). 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 Procedures Manual and Section 12.2.
g. Prior medications – Record all medications taken within 28 days of first dose of study treatment. 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.
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 6. For subjects who remain on treatment for greater than 1 year, ePROs will continue up to 1 year only.
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. ECOG and 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.

Trial Period:	Screening Phase		Treatment Cycles (3-Week 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 or per footnote	Every 12 weeks

q. Both PK and anti-pembrolizumab antibody for pembrolizumab arm only; pre-dose trough PK and anti-pembrolizumab antibody samples will be collected at Cycles 1, 2, 4, 8 and every 4 cycles thereafter, 30 days after discontinuation of study drug, and 3 months after discontinuation of study drug (or until the subject starts new anti-cancer therapy). All pre-dose trough samples should be drawn within 24 hours before infusion of pembrolizumab.

r. PK for pembrolizumab arm only; additional post-dose peak PK samples will be drawn within 30 minutes after end of pembrolizumab infusion at Cycles 1 and 8. An additional single PK sample should be drawn between 72 and 168 hours after Cycle 1 dosing.

s. Blood for correlative studies (includes blood, plasma and serum for DNA, RNA, and exploratory biomarkers) should be collected predose Cycle 1, Cycle 2, Cycle 3, and at treatment discontinuation. Detailed instructions with specific timepoints per sample are provided in the Procedures Manual.

t. The initial tumor imaging will be performed within 28 days prior to randomization date. Scans performed as part of routine clinical management are acceptable for use as the screening scan if they are of diagnostic quality and performed within 28 days prior to randomization date.

u. The first on-study imaging time point will be performed at 9 weeks (± 7 days) after randomization date 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. The same imaging technique should be used in a subject throughout the trial. On-study scans showing initial progression should be submitted immediately to the central imaging vendor and progressive disease should be verified by the central imaging and confirmed at least 4 weeks later prior to subject discontinuation from treatment.

v. In subjects who discontinue study therapy without centrally verified disease progression, a radiologic evaluation should be performed at the time of treatment discontinuation (i.e., date of 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 isn't mandatory.

w. Baseline tumor tissue from an archival tissue sample or newly obtained core or excisional biopsy (FNA not adequate) from subjects with oropharynx cancer must be tested locally or centrally for HPV status (if HPV status not known) prior to randomization for stratification. Baseline tumor tissue from a newly obtained sample must also be provided to the central vendor for PD-L1 biomarker testing prior to randomization for stratification. (Newly obtained tissue may be obtained up to 42 days prior to treatment initiation. Tissue beyond the 42-day window and up to 6 months may be considered with Sponsor consultation as long as no intervening systemic regimen has been taken.) Detailed instructions for tissue collection, process and shipment are provided in the Procedures 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.

x. It is most relevant and strongly recommended that ePROs are administered prior to drug administration, adverse event evaluation and disease status notification. Health economic assessment (HEA) to be completed by trained personnel prior to all other study procedures. All ePROs are to be performed prior to Cycle 1, Cycle 2, Cycle 3, Cycle 4 and every 2 cycles thereafter (e.g., Cycle 6, Cycle 8, Cycle 10) up to a year or End of Treatment, whichever occurs first, and the 30-day safety follow-up visit. If the subject does not complete the ePROs the MISS_MODE form must be completed to capture the reason the assessment was not performed.

y. This sample should be drawn for planned, exploratory genetic analysis of DNA and drug response unless there is either a documented law or regulation prohibiting collection, or unless the IRB/IEC does not approve of the collection of the sample for these purposes. If the sample is collected, any leftover extracted DNA will be stored for future biomedical research if the subject signs the FBR consent.

z. After Cycle 1, lab samples for T3, FT4, and TSH can be collected ±3 days before/after the scheduled time point. T3 or FT3 can be assayed based on local standards.

6.1.2 Standard Treatment Arm – Subjects Receiving Methotrexate, Docetaxel, or Cetuximab

Trial Period:	Screening Phase		Treatment Cycles (3-Week Cycles)[a]																		End of Treat-ment	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]
Treatment Day			1	8	15	1	8	15	1	8	15	1	8	15	1	8	15	1	8	15				
Scheduling Window (Days)[d]:	-42 to -1	-28 to -1	+3[d]	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of discon	30 days post discon	Every 6 weeks post discon	Every 12 weeks
Administrative Procedures																								
Informed Consent[e]	X																							
Informed Consent for Future Biomedical Research[f]	X																							
Inclusion/Exclusion Criteria		X																						
Subject Identification Card	X																							
Demographics and Medical History		X																						
Prior and Concomitant Medication Review[a,g]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Trial Treatment Administration[a]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Post-study Anticancer Therapy Status																							X	X
Survival Status[c]			< ---------- >																					X

Trial Period:	Screening Phase		Treatment Cycles (3-Week Cycles)[a]																		End of Treat-ment	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]
Treatment Day			1	8	15	1	8	15	1	8	15	1	8	15	1	8	15	1	8	15				
Scheduling Window (Days)[d]:	-42 to -1	-28 to -1	+3[d]	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of discon	30 days post discon	Every 6 weeks post discon	Every 12 weeks
Clinical Procedures/Assessments																								
Review Adverse Events[a,h]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[i]	X[i]	
12-Lead Electrocardiogram (Local)		X																						
Full Physical Examination		X																			X			
Directed Physical Examination			X			X			X			X			X			X						
Vital Signs and Weight[a,k]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
ECOG Performance Status[n]		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																						

Trial Period:	Screening Phase		Treatment Cycles (3-Week Cycles)[a]																		End of Treat-ment	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]
Treatment Day			1	8	15	1	8	15	1	8	15	1	8	15	1	8	15	1	8	15				
Scheduling Window (Days)[d]:	-42 to -1	-28 to -1	+3[d]	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of discon	30 days post discon	Every 6 weeks post discon	Every 12 weeks
CBC with Differential[a,o]		X[n]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[p]		
Chemistry Panel[a,o]		X[n]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[p]		
Urinalysis[o]		X[n]				X						X						X[j]				X[p]		
T3, FT4 and TSH[x]		X[n]				X						X						X[j]				X[p]		
Laboratory Procedures/Assessments: analysis performed by CENTRAL laboratory																								
Blood for Genetics[w]			X																					
Correlative Blood Samples[q]			X			X			X												X			
Efficacy Measurements																								
Tumor Imaging		X[r]										X[s]						X[s]			X[b, s, t]		X	

Trial Period:	Screening Phase		Treatment Cycles (3-Week Cycles)[a]																		End of Treat-ment	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]
Treatment Day			1	8	15	1	8	15	1	8	15	1	8	15	1	8	15	1	8	15				
Scheduling Window (Days)[d]:	-42 to -1	-28 to -1	+3[d]	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of discon	30 days post discon	Every 6 weeks post discon	Every 12 weeks
Tumor Tissue Collection																								
Archival or Newly Obtained Tissue Collection for Subjects with Oropharynx Cancer Tested Locally or Centrally for HPV Status for Stratification (newly obtained may be obtained 42 days prior to treatment initiation)[u]	X																							

Trial Period:	Screening Phase		Treatment Cycles (3-Week Cycles)[a]																		End of Treat-ment	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]
Treatment Day			1	8	15	1	8	15	1	8	15	1	8	15	1	8	15	1	8	15				
Scheduling Window (Days)[d]:	-42 to -1	-28 to -1	+3[d]	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of discon	30 days post discon	Every 6 weeks post discon	Every 12 weeks
Newly Obtained Tissue Collection for Biomarker Analysis (tested centrally) On all Subjects Prior to Randomization for Stratification (may be obtained 42 days prior to treatment initiation)[u]	X																							
Patient Reported Outcomes (ePROs)																								
EuroQol EQ-5D			X[v]			X[v]			X[v]			X[j, v]						X[j, v]			X[v]	X[v]		
EORTC QLQ-C30			X[v]			X[v]			X[v]			X[j, v]						X[j, v]			X[v]	X[v]		
EORTC QLQ-H&N 35			X[v]			X[v]			X[v]			X[j, v]						X[j, v]			X[v]	X[v]		

Trial Period:	Screening Phase		Treatment Cycles (3-Week Cycles)[a]																		End of Treat-ment	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]
Treatment Day			1	8	15	1	8	15	1	8	15	1	8	15	1	8	15	1	8	15				
Scheduling Window (Days)[d]:	-42 to -1	-28 to -1	+3[d]	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of discon	30 days post discon	Every 6 weeks post discon	Every 12 weeks
Health Economic Assessment						X[v]			X[v]			X[j, v]						X[j, v]			X[v]	X[v]		

a. In general, assessments/procedures are to be performed prior to the treatment dose. Subjects receiving docetaxel will be dosed on Day 1 of each 3 week cycle and will not have visits/procedures on Day 8 or Day 15. Subjects receiving methotrexate or cetuximab will be dosed on Days 1, 8 and 15 of each 3 week cycle. Imaging should be performed at 9 weeks after randomization date and every 6 weeks thereafter (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 by radiologic imaging every 6 weeks (± 7 days) until (1) the start of new anti-cancer treatment, (2) disease progression, (3) death, or (4) the end of the study, whichever occurs first.
c. After the start of new anti-cancer treatment or documented disease progression 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 study. Upon Sponsor notification, all participants who do not/will not have a scheduled study visit or study contact during the Sponsor defined time period will be contacted for their survival status (excluding participants that have a death event previously recorded).
d. In general, the window for each visit is ± 3 days unless otherwise noted. Cycle 1 treatment should be given within 3 days of randomization.
e. Documented consent must be obtained prior to performing any protocol specified procedure. Results of a test performed prior to the subject signing consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame (e.g., within 28 days prior to the first dose of trial treatment). 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 Procedures Manual and Section 12.2.
g. Prior medications – Record all medications taken within 28 days of first dose of trial treatment. 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.
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 6. For subjects who remain on treatment for greater than 1 year, ePROs will continue up to 1 year only.
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.

Trial Period:	Screening Phase		Treatment Cycles (3-Week Cycles)[a]																		End of Treat-ment	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]
Treatment Day			1	8	15	1	8	15	1	8	15	1	8	15	1	8	15	1	8	15				
Scheduling Window (Days)[d]:	-42 to -1	-28 to -1	+3[d]	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of discon	30 days post discon	Every 6 weeks post discon	Every 12 weeks

n. ECOG and 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. Blood for correlative studies (includes blood, plasma and serum for DNA, RNA, and exploratory biomarkers) should be collected predose Cycle 1, Cycle 2, Cycle 3, and at treatment discontinuation. Detailed instructions with specific timepoints per sample are provided in the Procedures Manual.
r. The initial tumor imaging will be performed within 28 days prior to randomization date. Scans performed as part of routine clinical management are acceptable for use as the screening scan if they are of diagnostic quality and performed within 28 days prior to randomization date.
s. The first on-study imaging time point will be performed at 9 weeks (± 7 days) after randomization date and then every 6 weeks (± 7 days) thereafter or more frequently if clinically indicated. After 1 year, imaging time point will resume every 9 weeks (± 7 days). Imaging timing should follow calendar days and should not be adjusted for delays in cycle starts. The same imaging technique should be used in a subject throughout the trial. On-study scans showing initial progression should be submitted immediately to the central imaging vendor and progressive disease should be verified by the central imaging and confirmed at least 4 weeks later prior to subject discontinuation from treatment.
t. In subjects who discontinue study therapy without centrally verified disease progression, a radiologic evaluation should be performed at the time of treatment discontinuation (i.e., date of 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 isn't mandatory.
u. Baseline tumor tissue from an archival tissue sample or newly obtained core or excisional biopsy (FNA not adequate) from subjects with oropharynx cancer must be tested locally or centrally for HPV status (if HPV status not known) prior to randomization for stratification. Baseline tumor tissue from a newly obtained sample must also be provided to the central vendor for PD-L1 biomarker testing prior to randomization for stratification. (Newly obtained tissue may be obtained up to 42 days prior to treatment initiation. Tissue beyond the 42-day window, and up to 6 months, may be considered with Sponsor consultation as long as no intervening systemic regimen has been taken.) Detailed instructions for tissue collection, process and shipment are provided in the Procedures 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. It is most relevant and strongly recommended that ePROs are administered prior to drug administration, adverse event evaluation and disease status notification. Health economic assessment (HEA) to be completed by trained personnel prior to all <u>other</u> study procedures. All ePROs are to be performed prior to Cycle 1, Cycle 2, Cycle 3, Cycle 4 and every 2 cycles thereafter (e.g., Cycle 6, Cycle 8, Cycle 10) up to a year or End of Treatment, whichever occurs first, and the 30-day safety follow-up visit. If the subject does not complete the ePROs the MISS_MODE form must be completed to capture the reason the assessment was not performed.
w. This sample should be drawn for planned, exploratory genetic analysis of DNA and drug response unless there is either a documented law or regulation prohibiting collection, or unless the IRB/IEC does not approve of the collection of the sample for these purposes. If the sample is collected, any leftover extracted DNA will be stored for future biomedical research if the subject signs the FBR consent.
x. After Cycle 1, lab samples for T3, FT4, and TSH can be collected ±3 days before/after the scheduled time point. T3 or FT3 can be assayed based on local standards.

6.2 Second Course Phase (Retreatment) for Pembrolizumab Arm Only

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	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			
ECOG Performance Status	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[t]	X[n]		X[j]		X[j]			X[s]		
Laboratory Procedures/Assessments: analysis performed by CENTRAL laboratory										
Pharmacokinetics[p]	X	X		X				X[p]	X[p]	
Anti-pembrolizumab Antibodies[p]	X	X		X				X[p]	X[p]	
Efficacy Measurements										
Tumor Imaging[q]	X		X		X		X[r]		X[q]	

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 by radiologic imaging every 6 weeks (± 7 days) until (1) the start of new anti-cancer treatment, (2) disease progression, (3) death, or (4) the end of the study, whichever occurs first.

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	Every 12 weeks

c. After the start of new anti-cancer treatment or documented disease progression 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 study. Upon Sponsor notification, all participants who do not/will not have a scheduled study visit or study contact during the Sponsor defined time period will be contacted for their survival status (excluding participants that have a death event previously recorded).
d. 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.
p. Both PK and anti-pembrolizumab antibody for pembrolizumab arm only; Pre-dose trough PK and anti-pembrolizumab antibody samples will be collected at Cycles 1, 2, 4, 8 and every 4 cycles thereafter, 30 days after discontinuation of study drug, and 3 months after discontinuation of study drug (or until the subject starts new anti-cancer therapy). 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. 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 isn't mandatory.
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.
t. After Cycle 1, lab samples for T3, FT4, and TSH can be collected ±3 days before/after the scheduled time point. T3 or FT3 can be assayed based on local standards.

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 documented informed consent before performing any procedure related to the Future Biomedical Research sub-trial. A copy of the informed consent will be given to the subject.

7.1.1.2 Inclusion/Exclusion Criteria

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

7.1.1.3 Subject Identification Card

All subjects will be given a Subject Identification Card identifying them as participants in a research trial. The card will contain trial site contact information (including direct telephone numbers) to be utilized in the event of an emergency. The investigator or qualified designee will provide the subject with a Subject Identification Card immediately after the subject provides documented 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 clinical 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 28 days before the first dose of trial treatment. 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 randomly allocated and will receive a randomization number. The randomization number identifies the subject for all procedures occurring after randomization. Once a randomization number is assigned to a subject, it can never be re-assigned to another subject.

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

Investigators must choose a standard treatment (methotrexate, docetaxel, or cetuximab) prior to randomization and document the selection in the interactive voice/integrated web response system. When choosing a standard therapy, the investigator should refer to the Summary of Product Characteristics (with special consideration for any contraindications, special warnings and precautions of use), and/or follow local guidelines.

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

Interruptions from the protocol specified treatment plan for greater than 12 weeks between pembrolizumab doses on the pembrolizumab treatment arm 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 infused will be compared to the total volume prepared to determine compliance with each dose of pembrolizumab administered.

The instructions for preparing and administering pembrolizumab will be provided in the Pharmacy Manual. Treatment with standard therapies will be prepared and administered as per the approved product label.

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 Section 12.6). Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

For subjects receiving treatment with pembrolizumab all AEs of unknown etiology associated with pembrolizumab exposure should be evaluated to determine if 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 physician exam during the screening period. Clinically significant abnormal findings should be recorded as medical history. A full physical exam should be performed as specified in the Trial Flow Chart. After the first dose of trial treatment new clinically significant abnormal findings should be recorded as AEs.

7.1.2.2.2 Directed Physical Exam

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

7.1.2.3 Vital Signs

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

7.1.2.4 12-Lead Electrocardiogram (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 Section 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 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 consistently for an anatomic region 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 utilized if clinically appropriate. Imaging should include head, neck, chest and abdomen at all timepoints specified in the Trial Flow Chart. Imaging of the pelvis is optional. A CT from the vertex of the head to the thoracic inlet or a brain CT is strongly preferred. .

Local reading (investigator assessment with site radiology reading) based on RECIST 1.1 will be used to determine subject eligibility. The central imaging vendor will receive all images from the sites and verify progressive disease following site assessed progressive disease. 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. Although RECIST 1.1 references to maximum of 5 target lesions in total and 2 per organ, Merck allows maximum of 10 target lesions in total and 5 per organ, if clinically relevant to enable a broader sampling of tumor burden. All scheduled images for all study subjects from the sites will be submitted to the central imaging vendor. In addition, additional imaging (including other modalities) that are obtained at an unscheduled time point to determine disease progression, as well as imaging obtained for other reasons but captures radiologic progression, should be submitted to the central imaging vendor as well.

In addition, radiologic progression will be based on the independent central verification of progression, rather than site assessment. Expedited verification of radiologic progression as determined by central review (following site assessment of progression) will be communicated to the site. (See Section 7.1.2.6.3 below.)

7.1.2.6.1 Initial Tumor Imaging

Initial tumor imaging must be performed within 28 days prior to randomization. The site study team must review pre-trial images to confirm the subject has measurable disease per RECIST 1.1. The baseline imaging scan must be submitted to the central imaging vendor for retrospective confirmation of eligibility.

Scans performed as part of routine clinical management are acceptable for use as the screening scan if they are of diagnostic quality and performed within 28 days prior to randomization.

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 randomization date. Subsequent imaging should be performed every 6 weeks (42 days ± 7 days), or 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 (e.g. 6 weeks later), whichever is clinically indicated.

Imaging should continue to be performed until initial site-assessed disease progression is verified by the central imaging vendor, the start of new anti-cancer treatment, withdrawal of consent, death, or the end of the study, whichever occurs first. Disease progression may be confirmed by the site 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, date of disease progression and as a basis for all protocol guidelines related to disease status (e.g., discontinuation of study therapy). Initial scans showing site-assessed PD should be submitted to the central imaging vendor immediately and the site will be notified when the imaging vendor verifies disease progression using RECIST 1.1. Sites should also assess tumor response and progression per modified RECIST for subjects on both treatment arms and this data will be collected in the clinical database.

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

If imaging shows PD, tumor assessment should be repeated ≥ 4 weeks later at the site in order to confirm PD with the option of continuing treatment for clinically stable subjects (see Table 9). 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

In determining whether or not the tumor burden has increased or decreased, investigators should consider all target lesions as well as non-target lesions (please refer to the Procedures Manual). Subjects that are deemed clinically unstable are not required to have repeat imaging for confirmation. If radiologic progression is confirmed 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 according to the every 6 weeks (42 ± 7 days) schedule.

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 9 weeks (63 ± 7 days) after 1 year for subjects who discontinue trial treatment for reasons other than disease progression until the subject experiences disease progression by site assessment followed by central imaging verification or starts a new anti-neoplastic therapy.

7.1.2.7 Tumor Tissue Collection and Correlative Blood Sampling

Subjects with oropharynx cancer must have assessment of HPV status from tumor tissue prior to randomization (see Section 5.1.2).

> Note: Tumor p16 expression must be evaluated by local assessment by means of IHC analysis with CINtec® p16 Histology assay (Ventana Medical Systems Inc., and Roche Diagnostics International Ltd.) using 'Benchmark Ultra' autostainer and standard protocol. Positive p16 expression is defined as strong and diffuse nuclear and cytoplasmic staining in 70% or more of the tumor cells.
>
> Note: Subjects without available local p16 testing results may submit tumor tissue for central p16 testing.

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 status.

Blood for correlative biomarker studies (RNA and DNA) should be collected predose at Cycle 1, at Cycle 2, at Cycle 3 and at treatment discontinuation; blood for correlative samples (plasma and serum) should be collected at Cycle 1.

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

7.1.2.8 Patient Reported Outcomes (PROs)

The EuroQol EQ-5D, EORTC QLQ C-30, and EORTC QLQ-H&N35 questionnaires will be administered by trained site personnel and completed electronically by subjects prior to all other study procedures in the following order: EuroQol EQ-5D first, then EORTC QLQ C-30, and lastly the EORTC QLQ-H&N35 at the time points specified in the Trial Flow Chart. It is most relevant and strongly recommended that ePROs are administered prior to drug administration, adverse event evaluation and disease status notification.

The health economic assessment (HEA) form will be completed via an interview with the subject by qualified site personnel after the subject completes all other questionnaires. The form captures all non-study related health care contacts made throughout the trial.

7.1.3 Laboratory Procedures/Assessments

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

7.1.3.1 Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

Laboratory tests for hematology, chemistry and urinalysis are specified in Table 10.

Table 10 Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Blood	Serum β-human chorionic gonadotropin (β-hCG)a
Hemoglobin	Alkaline phosphatase	Glucose	PT (INR)
Platelet count	Alanine aminotransferase (ALT)	Protein	aPTT
WBC (total and differential)	Aspartate aminotransferase (AST)	Specific gravity	Total triiodothyronine (T3) or Free T3
Red Blood Cell Count	Bicarbonateb	Microscopic exam, if abnormal results are noted	Free thyroxine (T4)
Absolute Neutrophil Count	Calcium	Urine pregnancy testa	Thyroid stimulating hormone (TSH)
Absolute Lymphocyte Count	Chloride		
	Creatinine		Blood for correlative studies
	Glucose		PK (for subjects on the pembrolizumab arm only)
	Phosphorus		Anti-pembrolizumab Antibodies (for subjects on the pembrolizumab arm only)
	Potassium		
	Sodium		
	Total Bilirubin		
	Direct Bilirubin, if total bilirubin is elevated above the upper limit of normal		
	Total protein		
	Blood Urea Nitrogen		
	Lactate dehydrogenase (LDH)		
	Carbon dioxide (CO2 or bicarbonate)b		
	Uric acid		
	Ureac		

a Perform on women of childbearing potential only. Serum pregnancy test is preferred but urine test can be considered if serum not appropriate.
b If these tests are not done as part of standard of care in your region, then these tests do not need to be performed.
c Blood Urea Nitrogen is preferred; if not available urea may be tested.

Laboratory tests for screening should be performed within 10 days prior to the first dose of trial treatment. 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 and exposure of pembrolizumab in this indication, sample collections for analysis of anti-pembrolizumab antibodies (ADA) and PK are currently planned as shown in the Trial Flowchart (Sections 6.1.1 and 6.2). Blood samples for PK and ADA collected may be stored. Analysis will be performed only if required. If ongoing PK and/or ADA sampling is deemed to be 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 Procedures Manual. PK samples should only be drawn for subjects in the pembrolizumab arm.

7.1.3.2.2 Blood Collection for Anti-Pembrolizumab Antibodies

Sample collection, storage and shipment instructions for anti-pembrolizumab antibody samples will be provided in the Procedures Manual. Anti-pembrolizumab antibody samples should only be drawn for subjects in the pembrolizumab arm.

7.1.3.3 Future Biomedical Research

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

- Leftover DNA for future use
- 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 on the pembrolizumab arm who a) attain a CR or b) complete 24 months of treatment with pembrolizumab may discontinue treatment with the option of restarting treatment if they meet the criteria specified in Section 7.1.5.2.1. After discontinuing treatment following assessment of CR or 24 months of 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 with the study documentation as source documentation at the trial site.

Critical Equipment for this trial includes:

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

See protocol-specified guidance in the Administrative Binder and Procedures 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 randomization, 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.
- Archival tumor collection is not required to be obtained within 28 days prior to the first dose of trial treatment. Newly obtained tumor tissue may be obtained within 42 days of treatment initiation.

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

- Either
    - Stopped initial treatment with pembrolizumab after attaining an investigator-determined confirmed CR according to RECIST 1.1
        - Was treated for at least 24 weeks with pembrolizumab before discontinuing therapy
        - Received at least two treatments with pembrolizumab beyond the date when the initial CR was declared

OR

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

AND

- Experienced an investigator-determined confirmed radiographic disease progression after stopping their initial treatment with pembrolizumab
- Did not receive any anti-cancer treatment since the last dose of pembrolizumab
- 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. 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 (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 disease progression will move into the Follow-Up Phase and should be assessed every 6 weeks (42 ± 7 days) by radiologic imaging to monitor disease status. After 1 year, the imaging time point will occur every 9 weeks (± 7 days). The Sponsor may request survival status to be assessed at additional time points during the course of the study (not to exceed approximately 12 weeks). Every effort should be made to collect information regarding disease status until the start of new anti-cancer therapy, disease progression, death, end of study or if the subject begins retreatment with pembrolizumab as detailed in Section 7.1.5.2.1. Information regarding post-study anti-cancer treatment will be collected if new treatment is initiated.

Subjects who are eligible to receive retreatment with pembrolizumab according to the criteria in Section 7.1.5.2.1 will move from the Follow-Up Phase to the Second Course Phase when they experience disease progression. Details are provided in Section 6.2 – Trial Flow Chart for Retreatment with pembrolizumab.

7.1.5.3.3 Survival Follow-up

Once a subject experiences disease progression by site assessment and verified by central review 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.

The Sponsor may request survival status to be assessed at additional time points during the course of the study. For example, these additional assessments may be requested prior to an external DMC safety review, efficacy interim analysis, and/or final analysis. All subjects who do not have a death reported will be contacted at the time of the Sponsor's request.

7.1.5.4 Survival Status

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

7.2 Assessing and Recording Adverse Events

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily

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

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

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

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

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

All adverse events that occur after the consent form is signed but before randomization must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure. From the time of randomization 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 and as any dose ≥20% over the prescribed dose for the standard treatments. No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

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

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

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

7.2.2 Reporting of Pregnancy and Lactation to the Sponsor

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

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

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

7.2.3 Immediate Reporting of Adverse Events to the Sponsor

7.2.3.1 Serious Adverse Events

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

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

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

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

Refer to Table 11 for additional details regarding each of the above criteria.

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

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

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

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

7.2.3.2 Events of Clinical Interest

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

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

For the time period beginning at randomization through 14 days following cessation of treatment, any ECI, or follow up to an ECI, whether or not related to the Sponsor's product, must be reported within 24 hours to the Sponsor, either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

Events of clinical interest for this trial include:

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).

1. 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.

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

   Subjects should be assessed for possible ECIs prior to each dose. Lab results should be evaluated and subjects should be asked for signs and symptoms suggestive of an immune-related event. Subjects who develop an ECI thought to be immune-related should have additional testing to rule out other etiologic causes. If lab results or symptoms indicate a possible 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 11 Evaluating Adverse Events

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

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

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

7.2.5 Sponsor Responsibility for Reporting Adverse Events

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

7.3 TRIAL GOVERNANCE AND OVERSIGHT

7.3.1 Scientific Advisory Committee

This trial was developed in collaboration with a Scientific Advisory Committee (SAC). The SAC comprises both Sponsor and non-Sponsor scientific experts who provide input with respect to trial design, interpretation of trial results and subsequent peer-reviewed scientific publications.

7.3.2 Executive Oversight Committee

The Executive Oversight Committee (EOC) comprises members of Sponsor Senior Management. The EOC will receive and decide upon any recommendations made by the Data Monitoring Committee (DMC) regarding the trial.

7.3.3 Data Monitoring Committee

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

The DMC will make recommendations to the EOC regarding steps to ensure both subject safety and the continued ethical integrity of the trial. Also, the DMC will review interim trial results, consider the overall risk and benefit to trial participants (see Section 8.2.9 - Interim Analyses) and recommend to the EOC if the trial should continue in accordance with the protocol.

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

8.0 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, but prior to any unblinding, changes 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, with the exception of a PRO analysis plan.

8.1 Statistical Analysis Plan Summary

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

8.1.1 Efficacy Analyses

The primary and key secondary endpoints, primary analysis population, and statistical methods that will be employed for the efficacy analyses are presented in Table 13. The intention-to-treat (ITT) population will serve as the primary analysis population in this study.

The primary efficacy endpoint is:

- Overall survival (OS) (i.e., time from randomization to death due to any cause) in all subjects (H1).

Key secondary efficacy endpoints include:

- OS in subjects with PD-L1 1% CPS (H2)
- ORR per RECIST 1.1 in all subjects (H3)
- ORR per RECIST 1.1 in subjects with PD-L1 1% CPS (H4)
- Progression-free-survival (PFS) per RECIST 1.1 in all subjects (H5)
- PFS per RECIST 1.1 in subjects with PD-L1 1% CPS (H6)

Baseline ECOG status (0 vs. 1), HPV status (HPV positive or negative for oropharynx cancers only; patients with non-oropharynx cancers are considered HPV negative by convention), and PD-L1 expression (PD-L1 Strong Positive vs. PD-L1 Not Strong Positive, where PD-L1 Strong Positive is defined as a PD-L1 tumor proportion score of ≥50% by IHC) will be the stratification variables in stratified analyses of all subject population.

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

8.1.2 Safety Analyses

The All Subjects as Treated (ASaT) population will be employed for safety analyses.

8.1.3 Power and Sample Size

The study will randomize approximately 466 subjects stratified by ECOG performance status (0 vs. 1), HPV status (HPV+ or HPV- for subjects with oropharynx cancer, HPV- for subjects without oropharynx cancer), and PD-L1 status (PD-L1 Strong Positive vs. PD-L1 Not Strong Positive) with a 1:1 ratio into the pembrolizumab arm and the standard treatment arm. The sample size calculation is determined by OS events in all subjects.

The final OS analysis in all subjects (H1) will be carried out after approximately 340 deaths have occurred between the pembrolizumab arm and standard treatment arm. With 340 events, the study provides 90% power to demonstrate superiority in OS of pembrolizumab relative to standard therapy at the alpha=2.5% (one-sided) level assuming proportional hazards with a true HR of 0.7. The sample size calculation is based on the following assumptions: 1) overall survival follows an exponential distribution with a median of 6.2 months in the control arm; 2) the hazard ratio for OS between pembrolizumab and control is 0.70 (deemed to be clinically meaningful in this population); 3) an enrollment period of 16 months; and 4) a yearly discontinuation from trial rate of 5%.

The family wise type I error rate for this study is strictly controlled at 2.5% (one-sided) for testing OS in all subjects. There are three planned analyses of OS in all subjects. If the OS analysis is successful in all subjects, then the key secondary hypotheses will be tested. Additional details are provided in Section 8.2.6 Multiplicity.

8.1.4 Interim Analysis

There will be two interim analyses for OS. Results of the interim analysis will be reviewed by the external data monitoring committee (DMC).

Further details of interim analyses are provided in Section 8.2.9 Interim Analysis and Table 15 as well as in the DMC Charter.

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.

The IVRS vendor will generate the randomized allocation schedule(s) for study treatment assignment for this protocol, and the randomization will be implemented in IVRS.

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

The study team at the Sponsor consisting of clinical, statistical, statistical programming and data management personnel, will be blinded to subject-level PD-L1 biomarker results. An

unblinded Sponsor clinical scientist, unblinded data management personnel, unblinded Sponsor statistician and unblinded Sponsor statistical programmer will have access to the subject-level PD-L1 results for the purpose of data review and informing the timing of the interim analyses and will have no other responsibilities associated with the study and have no access to the treatment allocation. A summary of PD-L1 biomarker prevalence may be provided to the study team at the Sponsor by the IVRS vendor or the unblinded Sponsor statistician.

Access to the allocation schedule and the subject-level PD-L1 results for summaries or analyses for presentation to the DMC will be restricted to an unblinded external statistician, and, as needed, an external scientific programmer performing the analysis, who will have no other responsibilities associated with the study.

Treatment-level results for the interim OS analysis in all subjects and PD-L1 1% CPS subjects will be provided by the external unblinded statistician to the DMC. The DMC will serve as the primary reviewer of the results of the OS analyses and will make recommendations for discontinuation of the study or modification to an Executive Oversight Committee of the SPONSOR.

If the DMC recommends modifications to the design of the protocol or discontinuation of the study, this Executive Oversight Committee may be unblinded to results at the treatment level in order to act on these recommendations. Limited additional SPONSOR personnel may be unblinded to the treatment level results of the OS analyses, if required, in order to act on the recommendations of the DMC or facilitate regulatory filing after the OS analyses. The extent to which individuals are unblinded with respect to results of interim analyses will be documented. Additional logistical details and data monitoring guidance will be provided in the DMC Charter. Key aspects of the interim analyses are described in Section 8.2.9.

Prior to final study unblinding, the external unblinded statistician will not be involved in any discussions regarding modifications to the protocol, statistical methods, identification of protocol violators, or data validation efforts after the OS analysis.

8.2.2 Hypotheses/Estimation

Objectives and hypotheses of the study are stated in Section 3.

8.2.3 Analysis Endpoints

8.2.3.1 Efficacy Endpoints

Primary

Overall Survival

Overall Survival (OS) is defined as the time from randomization to death due to any cause. Subjects without documented death at the time of the final analysis will be censored at the date of the last follow-up.

Secondary

Key Secondary Endpoints

Progression-free survival (PFS) - RECIST 1.1 by blinded independent radiology review

Progression-free-survival (PFS) is defined as the time from randomization to the first documented disease progression per RECIST 1.1 based on blinded independent radiology review or death due to any cause, whichever occurs first. See Section 8.2.5.1.2 for definition of censoring.

Supportive analyses of PFS will be conducted using site radiology review.

Objective Response Rate (ORR) – RECIST 1.1 by blinded independent radiology review

Objective response rate is defined as the proportion of the subjects in the analysis population who have a complete response (CR) or partial response (PR). Responses are based upon blinded independent radiology review per RECIST 1.1.

Supportive analyses of ORR will be conducted using site radiology review.

Other Secondary Endpoints

Time to Progression (TTP) – RECIST 1.1 by blinded independent radiology review

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

Supportive analyses of TTP will be conducted using site radiology review.

Duration of Response – RECIST 1.1 by blinded independent radiology review

For subjects who demonstrated confirmed CR or PR, duration of response is defined as the time from first documented evidence of CR or PR until disease progression or death. Subjects who are alive, have not progressed, have not initiated new anti-cancer treatment, and have not been determined to be lost to follow-up are considered ongoing responders at the time of analysis.

Supportive analyses of response duration will be conducted using site radiology review.

Progression-free survival (PFS) – modified RECIST by blinded independent radiology review

Modified RECIST is similar to RECIST 1.1 with the exception that a confirmation assessment of PD (at least 4 weeks after the initial PD assessment) is required for subjects who remain on treatment following a documented PD per RECIST 1.1. Subjects who discontinue treatment following a documented PD assessment per RECIST 1.1 will be counted as having disease progression on the date of the documented PD assessment. See

Section 8.2.5.1.1 for definition of censoring and section 4.2.3.1 for a more detailed definition of modified RECIST criteria.

Exploratory

Exploratory endpoints of this study include but are not limited to exploratory candidate biomarkers predictive of response to treatment, patient-reported outcomes (PROs), and PFS2.

PROs while on treatment and post-discontinuation will be examined.

PFS2 is defined as the time from randomization to subsequent disease progression after initiation of new anti-cancer therapy, or death from any cause, whichever occurs first. The subsequent disease progression is assessed by investigator and may not follow response criteria for RECIST 1.1. If progression after next-line therapy cannot be measured, a PFS2 event is defined as discontinuation of next-line treatment or death from any cause, whichever occurs first. Subjects who are alive and for whom a PFS2 event has not been observed will be censored at the last time known to be alive and without a second disease progression.

8.2.3.2 Safety Endpoints

Safety measurements are described in Section 7.

8.2.4 Analysis Population

8.2.4.1.1 Efficacy Analysis Population

The analysis of efficacy endpoints are based on the intention-to-treat (ITT) population, i.e., subjects will be included in the treatment group to which they are randomized. Details on the approach to handling missing data are provided in Section 8.2.5 Statistical Methods. This definition of ITT population will be used in the efficacy analyses for all subjects and PD-L1 1% CPS subjects.

8.2.4.1.2 Safety Analysis Populations

The All Subjects as Treated (ASaT) population will be used for the analysis of safety data in this study. The ASaT population consists of all randomized subjects who received at least 1 dose of study treatment. Subjects will be included in the treatment group corresponding to the trial treatment they actually received for the analysis of safety data.

For most subjects this will be the treatment group to which they are randomized. Subjects who take incorrect study treatment for the entire treatment period will be included in the treatment group corresponding to the study treatment actually received. Any subject who receives the incorrect study medication for one cycle but receives the correct treatment for all other cycles will be analyzed according to the correct treatment group and a narrative will be provided for any events that occur during the cycle for which the subject is incorrectly dosed.

At least one laboratory or vital sign measurement obtained subsequent to at least one dose of trial 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 Section 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 (i.e., unadjusted) 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

The family wise type I error rate for this study is strictly controlled at 2.5% (one -sided).

The strategy to address multiplicity issues with regard to multiple efficacy endpoints and multiple analyses is described in Section 8.2.6 and Section 8.2.9.

8.2.5.1.1 Overall Survival (OS)

The Kaplan-Meier method will be used to estimate the survival curves. The treatment difference in survival will be assessed by the stratified log-rank test. A stratified Cox proportional hazard model with Efron's method of tie handling will be used to assess the magnitude of the treatment difference (i.e., the hazard ratio). The hazard ratio and its 95% confidence interval from the stratified Cox model with a single treatment covariate will be reported. The same stratification factors used for randomization (see Section 5.4) will be applied to both the stratified log-rank test and the stratified Cox model for all subject population as well as PD-L1 1% CPS subject population. For the primary OS analysis in all subjects, an additional sensitivity analysis replacing the PD-L1 Strong Positive vs. Not Strong Positive by the PD-L1 1% CPS vs. Not 1% CPS in the stratified analysis will be performed.

Subjects in the standard therapy arm are expected to discontinue treatment earlier compared to subjects in the pembrolizumab arm and may switch to another anti PD-1 treatment following verification of progressive disease by central review. As an exploratory analysis, the Rank Preserving Structural Failure Time (RPSFT) model proposed by Robins and Tsiatis (1991) [49] will be used to adjust for the effect of crossover to other PD-1 therapies on OS. The RPSFT model provides a randomization-based estimate of treatment effect (RBEE) corrected for the bias induced by crossover. The 95% confidence intervals of the hazard ratio for OS after adjustment of the cross-over effect will be provided. The Kaplan-Meier estimates of the OS rate at 9 weeks, 27 weeks (when most cross-overs are likely to occur)

and other time points of interest will also be compared between the two treatment groups to explore the confounding effect of subsequent treatments.

8.2.5.1.2 Progression-Free Survival (PFS)

The non-parametric Kaplan-Meier method will be used to estimate the PFS curve in each treatment group. The treatment difference in PFS will be assessed by the stratified log-rank test. A stratified Cox proportional hazard model with Efron's method of tie handling will be used to assess the magnitude of the treatment difference (i.e., hazard ratio) between the treatment arms. The hazard ratio and its 95% confidence interval from the stratified Cox model with Efron's method of tie handling and with a single treatment covariate will be reported. The same stratification factors used for randomization (see Section 5.4) will be applied to both the stratified log-rank test and the stratified Cox model for all subjects and PD-L1 1% CPS subjects.

Since disease progression is assessed periodically, progressive disease (PD) can occur any time in the time interval between the last assessment where PD was not documented and the assessment when PD is documented. For the primary analysis, for the subjects who have PD, the true date of disease progression will be approximated by the date of the first assessment at which PD is objectively documented per RECIST 1.1 by central imaging vendor, regardless of discontinuation of study drug. Death is always considered as a confirmed PD event. Sensitivity analyses will be performed for comparison of PFS based on site assessment.

In order to evaluate the robustness of the PFS endpoint per RECIST 1.1 by blinded independent radiology review, two sensitivity analyses with different sets of censoring rules will be performed. The first sensitivity analysis is the same as the primary analysis except that it censors at the last disease assessment without PD when PD or death is documented after more than one missed disease assessment. The second sensitivity analysis is the same as the primary analysis except that it considers discontinuation of treatment or initiation of new anticancer treatment, whichever occurs later, to be a PD event for subjects without documented PD or death. The censoring rules for primary and sensitivity analyses are summarized in Table 12. We will also perform the following two additional PFS sensitivity analyses: 1) a PFS analysis using time to scheduled tumor assessment visit from randomization as opposed to actual tumor assessment time; 2) Finkelstein (1986)'s likelihood-based score test for interval-censored data, which modifies the Cox proportional hazard model for interval censored data, will be used as a supportive analysis for the PFS endpoint. The interval will be constructed so that the left endpoint is the date of the last disease assessment without documented PD and the right endpoint is the date of documented PD or death, whichever occurs earlier.

The proportional hazards assumption for the primary PFS analyses will be examined using both graphical and analytical methods. The proportional hazard assumption will be tested at the 0.05 significance level by including treatment**function*(time) as a factor in the model; nonsignificance ($p>0.05$) of this factor would suggest proportionality. A kernel-based estimate of log-hazard vs. time will be used to identify the appropriate functional form of the treatment effect-by-time interaction in a Cox PH model. Further, a visual examination of the

plot of the differences in the log cumulative hazards, $\log(H_2(t)) - \log(H_1(t))$ versus time for each level of treatment group will also be examined. If the proportional hazards model assumption holds then each curve should be roughly constant and parallel to the horizontal axis.

To account for the possible non-proportional hazards effect associated with immunotherapies, a supportive analysis will be conducted using a test for the restricted mean survival time (RMST) proposed by Uno, Tian, et al [50] for equality of two survival functions based on weighted differences of Kaplan-Meier curves. Thus, the PFS within each treatment group will be estimated using this approach, the 95% confidence intervals for the difference will be computed, and a test for differences between treatment groups will be performed. The cutoff for determining the RMST will be the last month for which at least 30 subjects within each treatment group are still at risk.

In addition, it is likely that a parametric model will fit data well and can be used as an alternative approach to comparing treatment group event rates over time. A Weibull model that allows the shape parameter to be a function of the covariates can also be used to examine the proportional hazards assumption where event rates change over time [51]; these will be fit with the gamlss.cens R package (package and reference are available the R library at http://cran.r-project.org). Other supportive analyses may include a cure model to compare treatment groups.

One key assumption for the stratified Cox proportional hazard model is that the hazard ratio (HR) is constant across strata. If strong departures from constant HR are observed in the stratified PFS analysis for all subjects, a sensitivity analysis may be performed using the two-step weighted Cox model approach by Mehrotra et al [52]. In this approach, the treatment effect is estimated within each stratum and the stratum-specific estimates are subsequently combined using sample size weights.

Table 12 Censoring rules for Primary and Sensitivity Analyses of PFS

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

8.2.5.1.3 Objective Response Rate (ORR)

Stratified Miettinen and Nurminen's method with strata weighting by sample size will be used for comparison of the objective response rates between the treatment groups. A 95% confidence interval for the difference in response rates between the pembrolizumab arm and the standard therapy arm will be provided. The same stratification factors used for randomization (see Section 5.4) will be applied to the analysis.

ORR by site radiology assessment and ORR in the subgroup of subjects with PD-L1 1% CPS will be analyzed using the same approach as the primary ORR analysis.

8.2.5.1.4 Duration of Response

If sample size permits, response duration will be summarized descriptively using Kaplan-Meier medians and quartiles. Only the subset of subjects who show a complete response or partial response will be included in this analysis. Response duration will be assessed using RECIST 1.1 separately by independent radiology review and by site radiology review.

8.2.5.1.5 Exploratory analyses

An exploratory analysis of PFS2 will be conducted using the same methods as for the secondary analysis of PFS. The non-parametric Kaplan-Meier method will be used to

estimate the PFS2 curve in each treatment group. The treatment difference in PFS2 will be assessed by the stratified log-rank test. A stratified Cox proportional hazard model with Efron's method of tie handling will be used to assess the magnitude of the treatment difference (i.e., hazard ratio) between the treatment arms. The hazard ratio and its 95% confidence interval from the stratified Cox model with Efron's method of tie handling and with a single treatment covariate will be reported. The same stratification factors used for randomization (see Section 5.4) will be applied to both the stratified log-rank test and the stratified Cox model for all subjects and PD-L1 1% CPS subjects.

Exploratory analyses of the treatment effect comparing pembrolizumab to standard treatment for OS, PFS, and ORR using RECIST 1.1 as assessed by blinded independent radiology review in the subgroup of subjects with strongly positive PD-L1 expression defined by ≥50% TPS will be carried out.

EORTC QLQ-C30, EORTC QLQ H&N35, and EQ-5D will be summarized as part of the exploratory analysis. Longitudinal and descriptive data analysis will be used to evaluate patient-reported outcomes. Several approaches will be considered to address the issue of informative missing data: (i) truncating the analysis observation period at the visit closest to median duration of treatment in the comparator arm, (ii) hierarchical pattern mixture models incorporating reason for missingness (a model that treats disease progression as a time-varying covariate) and (iii) multiple imputation methods. The difference in PRO score for progressed patients compared to patients with no radiographic evidence of tumor progression will be evaluated within each treatment arm. For HEA, descriptive statistics by treatment group will include total counts of each type of healthcare contact, as well as the total number of hospital days. The detailed PRO analysis plan will be included in a separate document.

Additional exploratory analyses of the relationship between treatment and predictive biomarkers predictive of response will be summarized using descriptive statistics.

Table 13 Efficacy Analysis Methods for Primary and Key Secondary Efficacy Endpoints

Endpoint/Variable (Description, Time Point)	Statistical Method	Analysis Population	Missing Data Approach
Primary Hypothesis 1 (H1)			
OS	Testing: Stratified Log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT in all subjects	Censored at date last known alive
Key Secondary Hypothesis 2 (H2)			
OS	Testing: Stratified Log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT in PD-L1 1% CPS subjects	Censored at date last known alive
Key Secondary Hypothesis 3 (H3)			
ORR (RECIST 1.1) by independent radiology review	Stratified Miettinen and Nurminen method with strata weighting by sample size	ITT in all subjects	Missing response considered non-responder
Key Secondary Hypothesis 4 (H4)			
ORR (RECIST 1.1) by independent radiology review	Stratified Miettinen and Nurminen method with strata weighting by sample size	ITT in PD-L1 1% CPS subjects	Missing response considered non-responder
Key Secondary Hypothesis 5 (H5)			
PFS (RECIST 1.1) by independent radiology review	Testing: Stratified Log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT in all subjects	• Primary Approach • Sensitivity Analysis 1 • Sensitivity Analysis 2 More details available in Table 12
Key Secondary Hypothesis 6 (H6)			
PFS (RECIST 1.1) by independent radiology review	Testing: Stratified Log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT in PD-L1 1% CPS subjects	• Primary Approach • Sensitivity Analysis 1 • Sensitivity Analysis 2 • More details available in Table 12

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, vital signs, and ECG measurements.

Time to Grade 3-5 AE

Time to first Grade 3-5 AE is defined as the time from the first day of study drug to the first event of Grade 3-5 AE. For patients without a Grade 3-5 AE, the time to first Grade 3-5 AE is censored at 30 days post last study dose. The Kaplan-Meier method will be used to estimate the curve of time to first Grade 3-5 AE. The treatment difference in time to first Grade 3-5 AE will be assessed by the log-rank test. A Cox proportional hazard model with Efron's method of tie handling will be used to assess the magnitude of the treatment difference (i.e., the hazard ratio). The hazard ratio and its 95% confidence interval from the Cox model with a single treatment covariate will be reported.

The analysis of safety results will follow a tiered approach (Table 14). The tiers differ with respect to the analyses that will be performed. Safety parameters or adverse experiences of special interest that are identified *a priori* constitute “Tier 1” safety endpoints that will be subject to inferential testing for statistical significance with p-values and 95% confidence intervals provided for between-group comparisons. Other safety parameters will be considered Tier 2 or Tier 3. Tier 2 parameters will be assessed via point estimates with 95% confidence intervals provided for between-group comparisons; only point estimates by treatment group are provided for Tier 3 safety parameters.

Adverse experiences (specific terms as well as system organ class terms) and predefined limits of change in laboratory, vital signs, and ECG parameters that are not pre-specified as Tier-1 endpoints will be classified as belonging to "Tier 2" or "Tier 3", based on the number of events observed. Membership in Tier 2 requires that at least 4 subjects in any treatment group exhibit the event; all other adverse experiences and predefined limits of change will belong to Tier 3.

The threshold of at least 4 events was chosen because the 95% confidence interval for the between-group difference in percent incidence will always include zero when treatment groups of equal size each have less than 4 events and thus would add little to the interpretation of potentially meaningful differences. Because many 95% confidence intervals may be provided without adjustment for multiplicity, the confidence intervals should be regarded as a helpful descriptive measure to be used in review, not a formal method for assessing the statistical significance of the between-group differences in adverse experiences and predefined limits of change.

Continuous measures such as changes from baseline in laboratory, vital signs, and ECG parameters that are not pre-specified as Tier-1 endpoints will be considered Tier 3 safety parameters. Summary statistics for baseline, on-treatment, and change from baseline values will be provided by treatment group in table format.

For this protocol, there are no Tier 1 events. The broad clinical and laboratory AE categories consisting of the percentage of subjects with any AE, a drug related AE, a serious AE, a Grade 3-5 AE, an AE which is both Grade 3-5 and drug-related, an AE which is both drug-related and serious, an AE which results in dose modification, and who discontinued due to an AE will be considered Tier 2 endpoints. P-values (Tier 1 only) and 95% confidence intervals (Tier 1 and Tier 2) will be provided for between-treatment differences in the percentage of subjects with events; these analyses will be performed using the Miettinen and Nurminen method (1985) [53], an unconditional, asymptotic method.

To properly account for the potential difference in follow-up time between the study arms, which is expected to be longer in the pembrolizumab arm, AE incidence density adjusted for treatment exposure analyses may be performed as appropriate. Based on emerging external data, the supportive analysis strategy for safety parameters may be modified to improve the integrity and efficiency of the design. Should this happen, the change will be documented elsewhere, if not in a protocol amendment, at the earliest time before any unblinding of the data.

Table 14 Analysis Strategy for Safety Parameters

Safety Tier	Safety Endpoint	p-Value	95% CI for Treatment Comparison	Descriptive Statistics
Tier 1	None	X	X	X
Tier 2	Any AE		X	X
	Any Grade 3-5 AE		X	X
	Any Serious AE		X	X
	Any Drug-Related AE		X	X
	Any Serious and Drug-Related AE		X	X
	Any Grade3-5 and Drug-Related AE		X	X
	Dose Modification due to AE		X	X
	Discontinuation due to AE		X	X
	Death		X	X
	Specific AEs, SOCs (including ≥4 of subjects in one of the treatment groups)		X	X
Tier 3	Specific AEs, SOCs (incidence <4 of subjects in all of the treatment groups)			X
	Change from Baseline Results (Labs, ECGs, Vital Signs)			X

SOC = System Organ Class.

8.2.5.3 Summaries of Baseline Characteristics, Demographics, and Other Analyses

The comparability of the treatment groups for each relevant characteristic will be assessed by the use of tables and/or graphs. No statistical hypothesis tests will be performed on these characteristics. The number and percentage of subjects randomized, and the primary reason for discontinuation will be displayed. Demographic variables (such as age) and baseline

characteristics will be summarized by treatment either by descriptive statistics or categorical tables. The reasons for exclusion from the ITT population (if any) will be summarized.

8.2.6 Multiplicity

The family-wise type I error rate for this study is strongly controlled at 2.5% (one-sided) with full alpha allocated to the OS hypothesis in all subjects (H1). A Hwang-Shih-DeCani alpha-spending function with the gamma parameter (-4) and beta-spending function with the gamma parameter (-16) are constructed to implement group sequential boundaries that control the type I error rate as well as allow for non-binding futility analysis. Two interim analyses for OS in all subjects are planned in this trial and further details of the interim analysis strategy can be found in Section 8.2.9.

If the pembrolizumab arm is demonstrated to have a superior OS to the control arm for all subjects (H1) at any analysis, the alpha allocated at that analysis will be rolled into the OS hypothesis for PD-L1 1% CPS subjects to test H2. The ORR per RECIST 1.1 endpoints will be tested if H2 is rejected and PFS per RECIST 1.1 will be tested if the ORR endpoints are rejected in their respective populations. The hierarchical order for testing key secondary endpoints and alpha spending scheme according to the method of Maurer and Bretz (2013) [54] are illustrated in Figure 4.

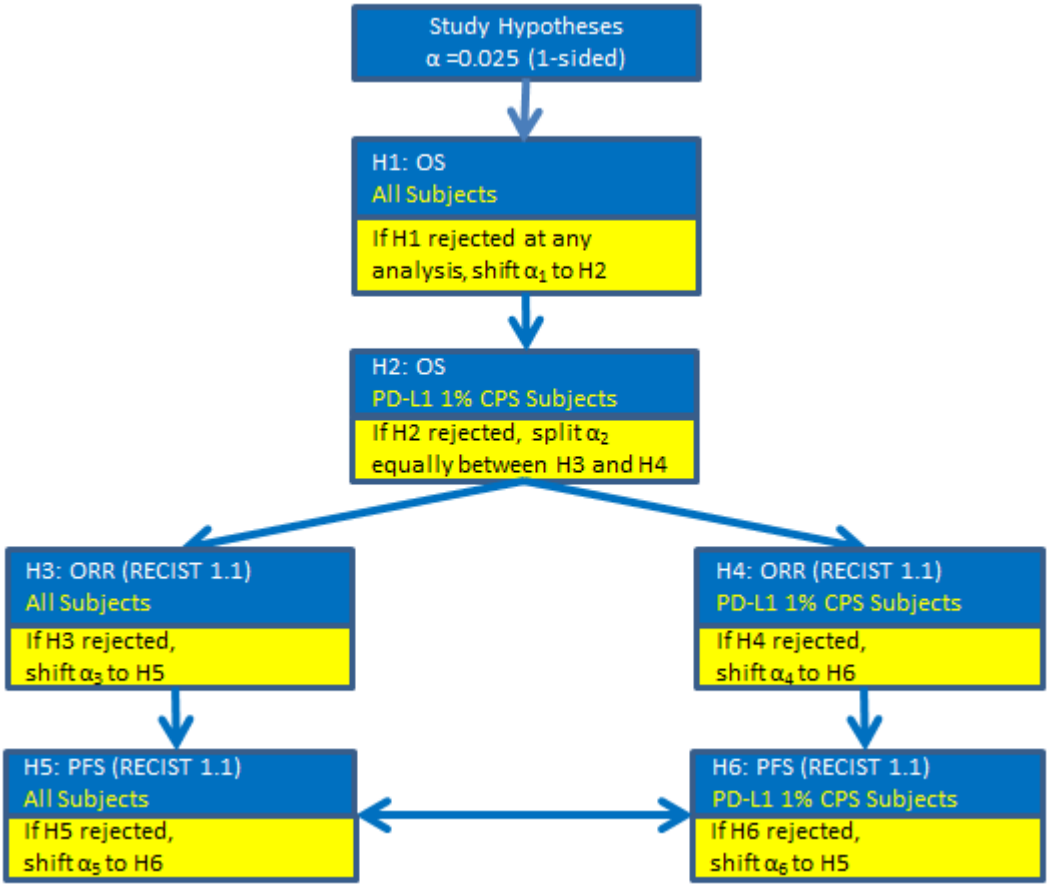

Figure 4 Type I Error Reallocation Strategy Following Closed Testing Principle

The ORR and PFS per RECIST 1.1 are planned to be tested twice at the first and second interim. 2% of alpha will be allocated to the first interim and 0.5% will be allocated to the second interim, and will be split evenly between all subjects and 1% CPS subjects: i.e. 1% alpha will be allocated to the first interim and 0.25% to the second interim for all subjects and the same for PD-L1 1% CPS subjects for ORR and PFS endpoints, following the sequential testing procedure illustrated above.

Based on emerging data external to this study [55, 56], the initial projected number of death events at the final analysis is revised in Amendment 11 onward to account for the delayed separation in the overall survival curves that have been observed with immunotherapies. Thus, additional follow-up time is incorporated into the trial to ensure that the final analysis is conducted at an appropriate time to characterize the potential benefit of immunotherapy.

With the delayed final analysis, the efficacy and futility spending functions remain unchanged. The information fractions based on the previously planned number of death events at the final analysis were used hence the alpha allocated to IA1 and IA2 were kept intact and the remaining alpha will be spent at the final analysis to ensure the type I error rate is strongly controlled at 2.5% (one-sided). The efficacy boundaries (nominal p-value and

boundary hazard ratio) at the final analysis will be calculated using the actual number of death events taking into account the correlation with the previous interim analysis.

8.2.7 Sample Size and Power Calculation

The study is event-driven and plans to randomize approximately 466 subjects with 1:1 ratio into the pembrolizumab arm and the standard therapy arm.

OS Analysis in All Subjects (H1): The final OS analysis in all subjects will be conducted after ~340 deaths have occurred between the pembrolizumab arm and the standard therapy arm. The final OS analysis is expected to occur at approximately twelve months after the last subject is enrolled in the study. This is to ensure adequate survival follow-up to account for the delayed separation in the OS curves that have been observed with immunotherapies. Under the proportional hazard assumption with 340 events at the final analysis, the study provides 90% power to demonstrate superiority in OS of pembrolizumab relative to standard therapy at the alpha=2.5% (one-sided) level with a true HR of 0.7. Success for OS at the final analysis approximately corresponds to an observed hazard ratio of < 0.80. The sample size calculation is based on the following assumptions: 1) OS follows an exponential distribution with a median of 6.2 months in the standard therapy arm, 2) hazard ratio between MK-3475 and standard therapy is 0.7, 3) an enrollment period of 16 months; and 4) a yearly discontinuation from trial rate of 5%. To further investigate the impact of the delayed separation of OS curve on the actual power, a simulation study was carried out using the current study design parameters from the above but with a piece-wise time varying hazard ratio: the hazard ratio was specified as 1, 0.73, 0.60, 0.55, 0.52, and 0.49 at the beginning of time intervals of month 0, 3.5, 5.5, 7.5, 9.5, and 11.5 since randomization respectively. With 1,000 simulations the overall study power with 340 events at the final analysis given the hazard ratio assumption above is approximately 77%.

The assumptions for the median OS of 6.2 months in the standard therapy arm are based on estimates of median OS from 2L and 3L trials of single agents [29; 30; 31; 32; 33; 34; 35; 36].

The sample size, power calculations, and simulations were performed in the software EAST and R (package “gsDesign”).

8.2.8 Subgroup Analyses and Effect of Baseline Factors

To determine whether the treatment effect is consistent across various subgroups, the estimate of the between-group treatment effect (with a nominal 95% CI) for the primary endpoint will be estimated and plotted within each category of the following classification variables:

- Stratification Factors:
  - PD-L1 subgroup (PD-L1 Strong Positive vs. Not PD-L1 Strong Positive)
  - HPV status (HPV positive vs. HPV negative)
  - ECOG status (0 vs. 1)

- Age category (≤65 vs. >65 years)
- Line of therapy (first line vs. second line vs. third line)
- Sex (female vs. male)
- Race (white vs. non-white)
- Geographic region of enrolling site (East Asia vs. non-East Asia)
- Smoking status (never vs. former vs. current)
- Brain metastasis status (baseline brain metastasis vs. no baseline brain metastasis)
- Investigators' choice of standard therapy identified prior to randomization

The consistency of the treatment effect will be assessed descriptively via summary statistics by category for the classification variables listed above.

8.2.9 Interim Analysis

There are two planned interim analyses. In this study, the futility bounds are non-binding, which means the bounds are considered guidance rather than strict bounds. Results of the interim analyses of OS for all subjects will be reviewed by a data monitoring committee (DMC). Further details of interim analyses are provided below and will be incorporated into the DMC Charter.

For OS in all subjects, a Hwang-Shih-DeCani alpha-spending function with the gamma parameter (-4) and beta-spending function with the gamma parameter (-16) are constructed to implement group sequential boundaries that control the type I error rate as well as allow for non-binding futility analysis. The actual boundary for each interim OS analysis will be determined from the number of OS events observed at the time of the data lock for the specified analysis using the alpha-spending function

Interim Analysis 1 for OS in all subjects (H1):

The first interim analysis will take place when approximately 144 OS events have occurred between the pembrolizumab arm and the standard therapy arm for all subjects at the alpha level determined by the spending function boundaries and actual number of OS events (Table 15). Success at the interim analysis 1 for the OS analysis corresponds to an approximate observed hazard ratio < 0.63 (approximately a 3.6-month improvement or greater in median OS) for all subjects. If H1 is rejected, the same alpha boundary determined by H1 will be used to test the first key secondary endpoint: OS in PD-L1 1% CPS subjects (H2). If H2 is rejected, ORR and PFS endpoints can be tested according to the rules for the sequential testing and alpha allocation detailed in Section 8.2.6 Multiplicity.

Interim Analysis 2 for OS in all subjects (H1):

The second interim analysis will take place when approximately 216 OS events have occurred between the pembrolizumab arm and the standard therapy arm for all subjects at the alpha level determined by the spending function boundaries and actual number of OS events.

Success at the interim analysis 2 for the OS analysis corresponds to an approximate observed hazard ratio < 0.72 (approximately a 2.4-month improvement or greater in median OS) for all subjects. If H1 is rejected, the same alpha boundary determined by H1 will be used to test the first key secondary endpoint: OS in PD-L1 1% CPS subjects (H2). If H2 is rejected, ORR and PFS endpoints can be tested according to the rules for the sequential testing and alpha allocation detailed in Section 8.2.6 Multiplicity.

Final Analysis for OS in all subjects (H1):

As mentioned in Section 8.2.6 and 8.2.7 the final analysis will be conducted when approximately 340 deaths have occurred between the pembrolizumab arm and the standard therapy arm for all subjects to allow for further follow-up in all subjects. This is expected to occur approximately twelve months after the last subject was enrolled in the study and to ensure adequate survival follow-up to account for delayed separation of the OS curves. At the final analysis the remaining alpha not spent at IA1 or IA2 will be used and the final analysis boundary values (nominal p-value and boundary hazard ratio) will be calculated using the actual number of death events taking into account the correlation with the previous interim analysis. Success at the final OS analysis corresponds to an approximate observed hazard ratio < 0.80. If H1 is rejected, the same alpha boundary determined by H1 will be used to test the first key secondary endpoint: OS in PD-L1 1% CPS subjects (H2). The ORR and PFS endpoints will not be tested formally at the final analysis.

Table 15 Summary of Sample size and Decision Guidance at the Interim and Final OS Analyses by Design

Analysis	**Criteria for Conduct of Analysis**		**Boundary**		
			Z statistics	p value (1-sided)	~Observed HR at boundary
IA 1: OS in all subjects (H1)	OS Events: 144	Efficacy	-2.75	0.0030	0.63
		Futility†	1.75	0.96	1.34
IA 2: OS in all subjects (H1)	OS Events: 216	Efficacy	-2.43	0.0075	0.72
		Futility†	0.157	0.56	1.02
Final Analysis: OS in all subjects (H1)	OS Events: 288	Efficacy	-2.01	0.022	0.79
		Futility	-2.01	0.022	0.79

IA = Interim Analysis.
†: Futility boundary is non-binding.

Table 16 Summary of Actual Boundaries at Interim and Expected Boundaries at Final Analyses with Extended Follow-up

Analysis	OS Events (Alpha Spent)		Boundary	
			p value (1-sided)	~Observed HR at boundary
IA 1: OS in all subjects (H1)	160 (0.0038§)	Efficacy	0.0038	0.65
		Futility†	0.92	1.2
IA 2: OS in all subjects (H1)	245 (0.0097§)	Efficacy	0.0120	0.75
		Futility†	0.277	0.93
Final Analysis: OS in all subjects (H1)	340‡ (0.0114)	Efficacy	0.0186	0.80
		Futility	0.0186	0.80

IA = Interim Analysis.
†: Futility boundary is non-binding.
‡: Expected to occur approximately 12 months after the last subject was enrolled to ensure adequate survival follow-up
§: Actual alpha spent at each interim analyses

8.2.10 Compliance (Medication Adherence)

Drug accountability data for trial treatment will be collected during the study. Compliance with trial treatment administration will be measured by subjects: 1) receiving unscheduled study agent infusions/injections; 2) missing an infusion/injection. Numbers and percentages of subjects and infusion/injection visits with any deviation in these measures will be reported for the ITT population.

8.2.11 Extent of Exposure

The extent of exposure will be summarized as duration of treatment in cycles. Dose intensity will also be summarized as appropriate.

9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.1 Investigational Product

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

Clinical Supplies will be provided by the Sponsor as summarized in Table 17.

Table 17 Product Descriptions

Product Name & Potency	Dosage Form
Pembrolizumab 25 mg / mL	Solution for Infusion
Cetuximab 5 mg / mL	Solution for Infusion
Methotrexate 25 mg / mL	Solution for infusion
Docetaxel 20 mg / mL	Solution for infusion

The cetuximab, methotrexate and docetaxel will be provided centrally by the Sponsor or locally by the trial site, subsidiary or designee, depending on local country operational or regulatory requirements. All other products will be provided locally by the trial site, subsidiary or designee.

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

9.2 Packaging and Labeling Information

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

All supplies will be provided open label. Pembrolizumab and cetuximab will be provided as non-kitted single vials or as single vials in a kit box. All other products will be provided as a kit with a single vial.

9.3 Clinical Supplies Disclosure

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

9.4 Storage and Handling Requirements

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

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

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

9.5 Returns and Reconciliation

The investigator is responsible for keeping accurate records of the clinical supplies received from the Sponsor or designee, the amount dispensed to and returned by the subjects and the amount remaining at the conclusion of the trial. For all trial sites, the local country Sponsor

personnel or designee will provide appropriate documentation that must be completed for drug accountability and return, 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.

For all trial sites, the local country Sponsor personnel or designee will provide appropriate documentation that must be completed for drug accountability and return.

9.6 Standard Policies

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

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

10.1 Confidentiality

10.1.1 Confidentiality of Data

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

10.1.2 Confidentiality of Subject Records

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

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

10.1.3 Confidentiality of Investigator Information

By signing this protocol, the investigator recognizes that certain personal identifying information with respect to the investigator, and all subinvestigators and trial site personnel,

may be used and disclosed for trial management purposes, as part of a regulatory submissions, and as required by law. This information may include:

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

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

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

10.1.4 Confidentiality of IRB/IEC Information

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

10.2 Compliance with Financial Disclosure Requirements

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

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

10.3 Compliance with Law, Audit and Debarment

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

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

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

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

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

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

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

when documents may be destroyed. The Sponsor will determine the minimum retention period and upon request, will provide guidance to the investigator when documents no longer need to be retained. The sponsor also recognizes that documents may need to be retained for a longer period if required by local regulatory requirements. All trial documents shall be made available if required by relevant regulatory authorities. The investigator must consult with and obtain written approval by the Sponsor prior to destroying trial and/or subject files.

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

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

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

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

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

10.4 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the Sponsor of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to the Clinical Trials Data Bank, http://www.clinicaltrials.gov. Merck, as Sponsor of this trial, will review this protocol and submit the information necessary to fulfill these requirements. Merck entries are not limited to FDAMA/FDAAA mandated trials. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

By signing this protocol, the investigator acknowledges that the statutory obligations under FDAMA/FDAAA are that of the Sponsor and agrees not to submit any information about this trial or its results to the Clinical Trials Data Bank.

10.5 Quality Management System

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

10.6 Data Management

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

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

10.7 Publications

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

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

the efficacy and safety measures, the statistical analysis plan, and any amendments relating to those sections. The Sponsor reserves the right to redact proprietary information.

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

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

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

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12.0 APPENDICES

12.1 Merck Code of Conduct for Clinical Trials

Merck*
Code of Conduct for Clinical Trials

I. Introduction

A. Purpose

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

B. Scope

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

II. Scientific Issues

A. Trial Conduct

1. Trial Design

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

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

2. Site Selection

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

3. Site Monitoring/Scientific Integrity

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

B. Publication and Authorship

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

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

III. Subject Protection

A. IRB/ERC review

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

B. Safety

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

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

C. Confidentiality

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

D. Genomic Research

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

IV. Financial Considerations

A. Payments to Investigators

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

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

B. Clinical Research Funding

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

C. Funding for Travel and Other Requests

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

V. Investigator Commitment

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

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

12.2 Collection and Management of Specimens for Future Biomedical Research

1. Definitions

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

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

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

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research

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

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

3. Summary of Procedures for Future Biomedical Research

a. Subjects for Enrollment

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

b. Informed Consent

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

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

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

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

c. eCRF Documentation for Future Biomedical Research Specimens

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

d. Future Biomedical Research Specimen Collections

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

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

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

4. Confidential Subject Information for Future Biomedical Research

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

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

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

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

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

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

5. Biorepository Specimen Usage

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

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

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

6. Withdrawal From Future Biomedical Research

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

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

7. Retention of Specimens

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

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

8. Data Security

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

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

9. Reporting of Future Biomedical Research Data to Subjects

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

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

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

10. Gender, Ethnicity and Minorities

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

11. Risks Versus Benefits of Future Biomedical Research

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

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

It is necessary for subject-related data (i.e., ethnicity, diagnosis, drug therapy and dosage, age, toxicities, etc.) to be re-associated to double coded specimens at the time of data analysis. These subject data will be kept in a separate, secure Merck database, and all specimens will be stripped of subject identifiers. No information concerning results

obtained from future biomedical research will be entered into clinical records, nor will it be released to outside persons or agencies, in any way that could be tied to an individual subject.

12. Self-Reported Ethnicity

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

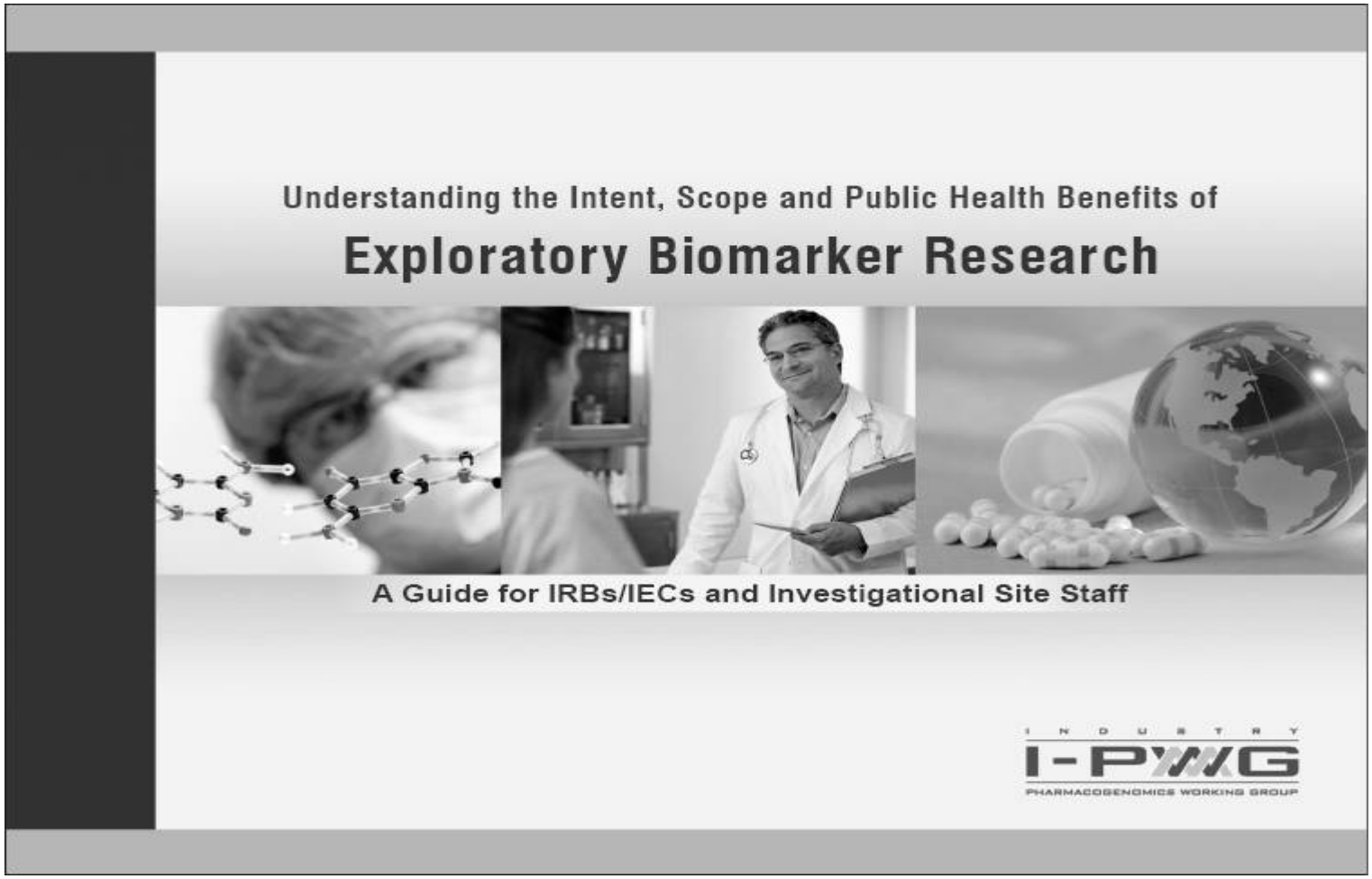
13. Questions

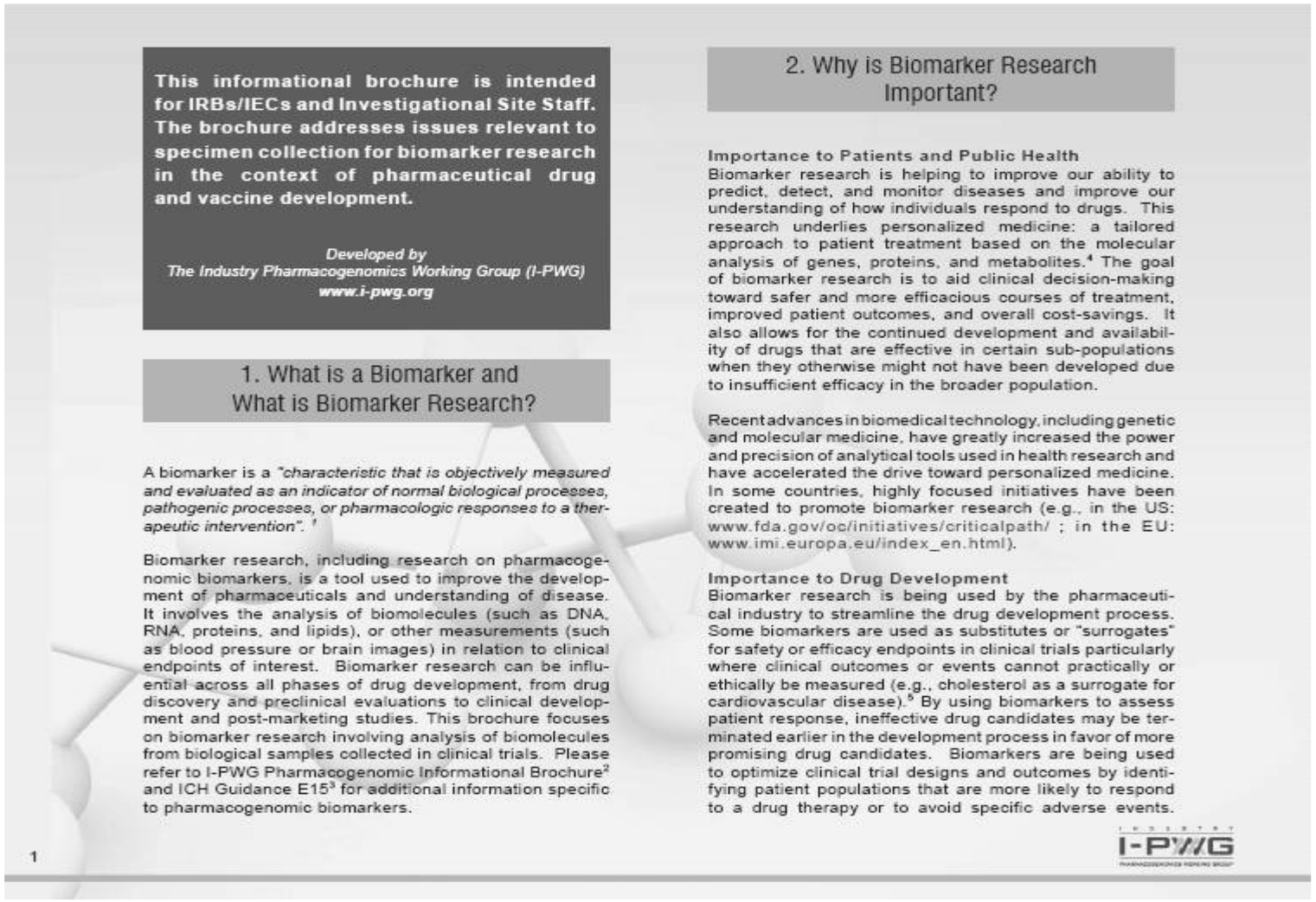
Any questions related to the future biomedical research should be e-mailed directly to clinical.specimen.management@merck.com.

14. 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?

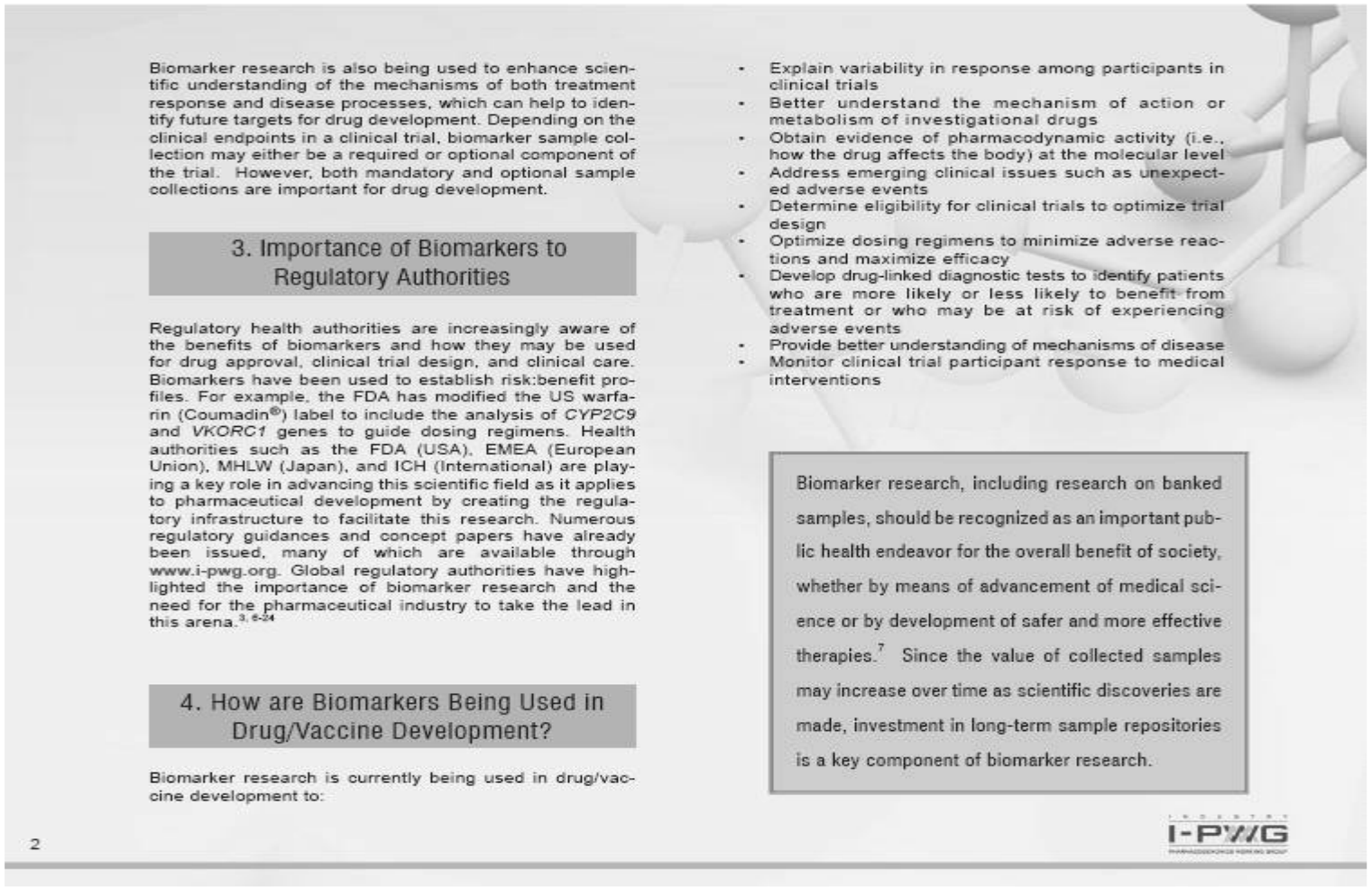
Importance to Patients and Public Health
Biomarker research is helping to improve our ability to predict, detect, and monitor diseases and improve our understanding of how individuals respond to drugs. This research underlies personalized medicine: a tailored approach to patient treatment based on the 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.

1

I-PWG


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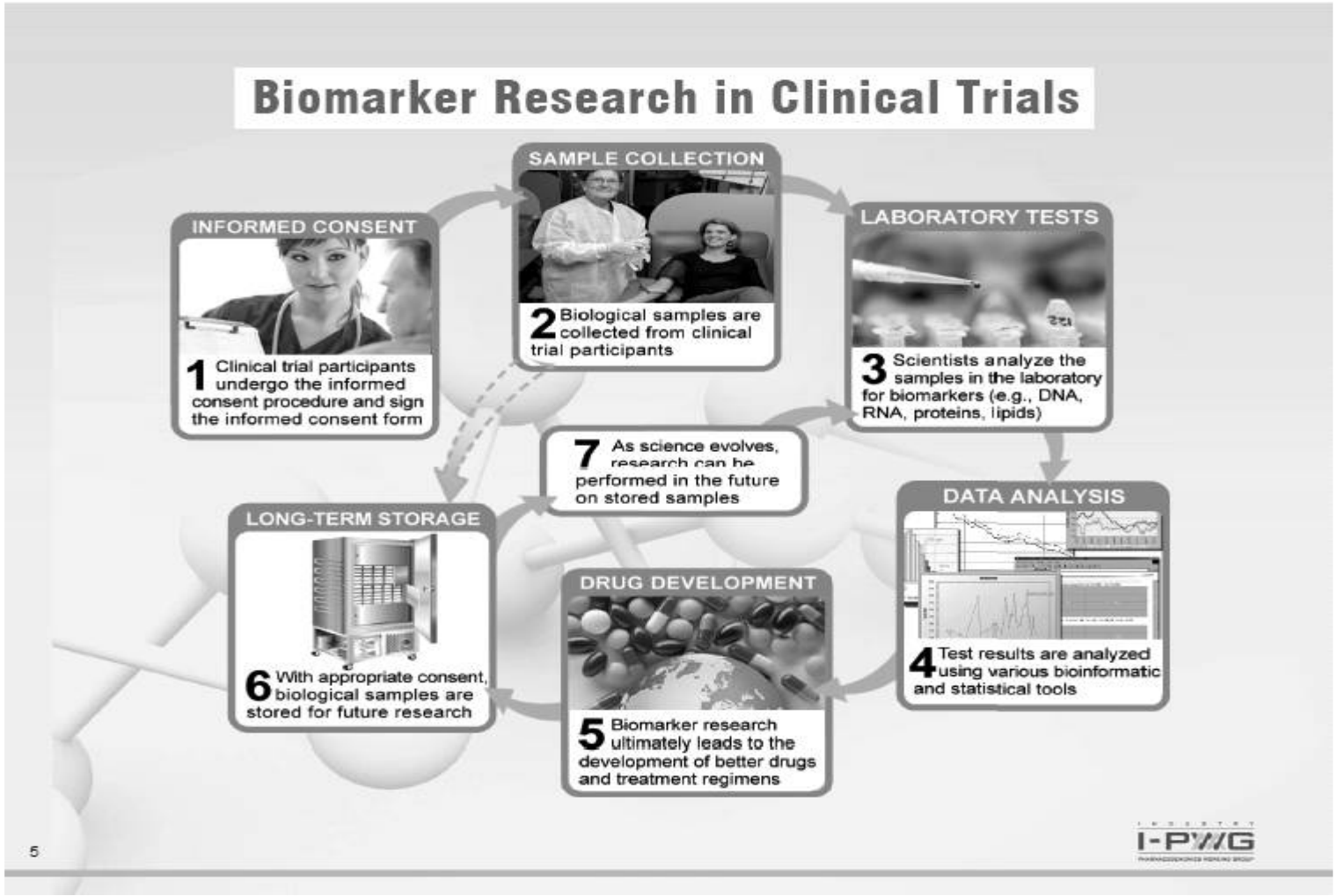
Biomarker Research in Clinical Trials
SAMPLE COLLECTION
2 Biological samples are collected from clinical trial participants
INFORMED CONSENT
1 Clinical trial participants undergo the informed consent procedure and sign the informed consent form
LABORATORY TESTS
3 Scientists analyze the samples in the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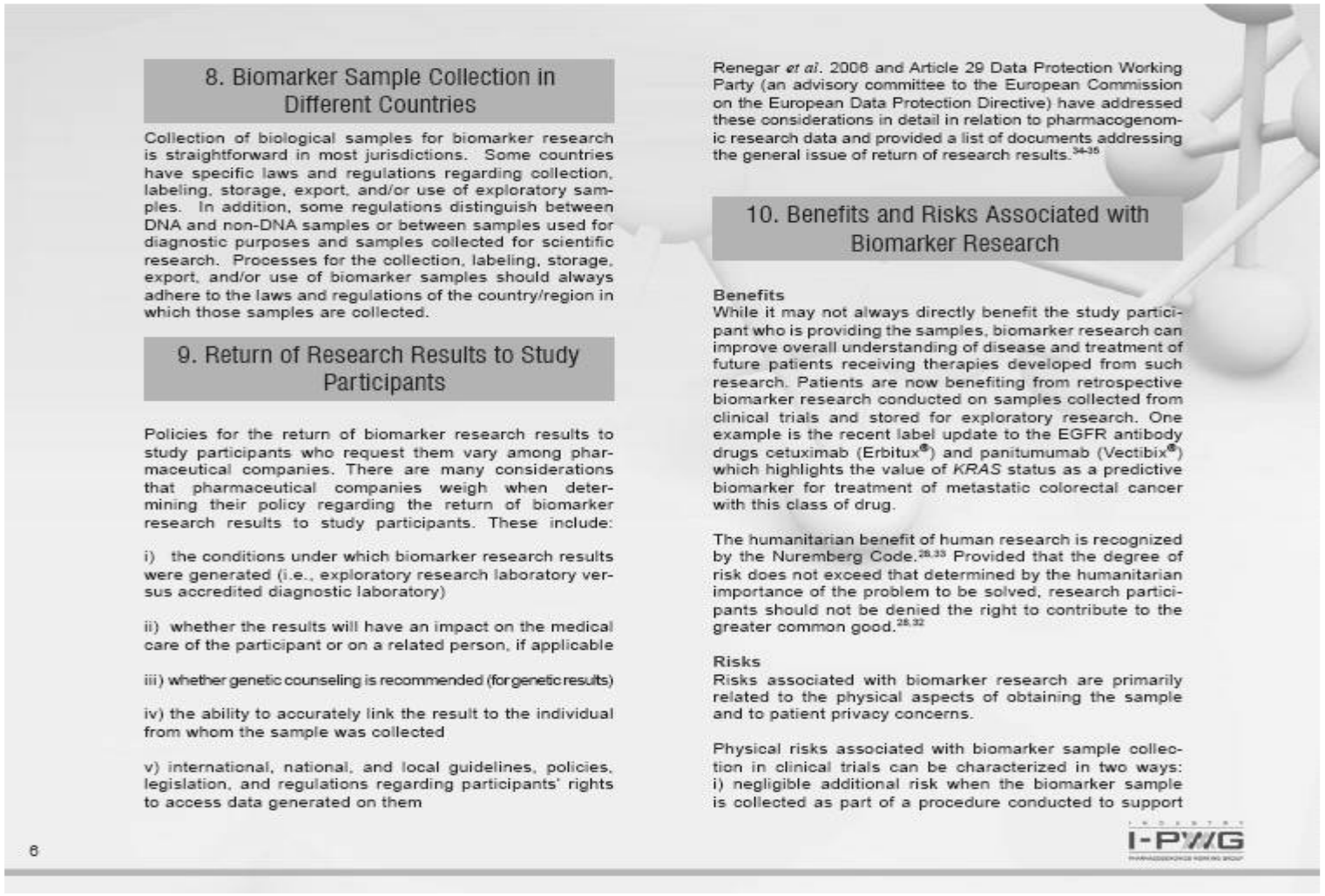

8. Biomarker Sample Collection in Different Countries

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

9. Return of Research Results to Study Participants

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

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

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

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

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

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

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

10. Benefits and Risks Associated with Biomarker Research

Benefits

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

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

Risks

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

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

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

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

11. Privacy, Confidentiality, and Patient Rights

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

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

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

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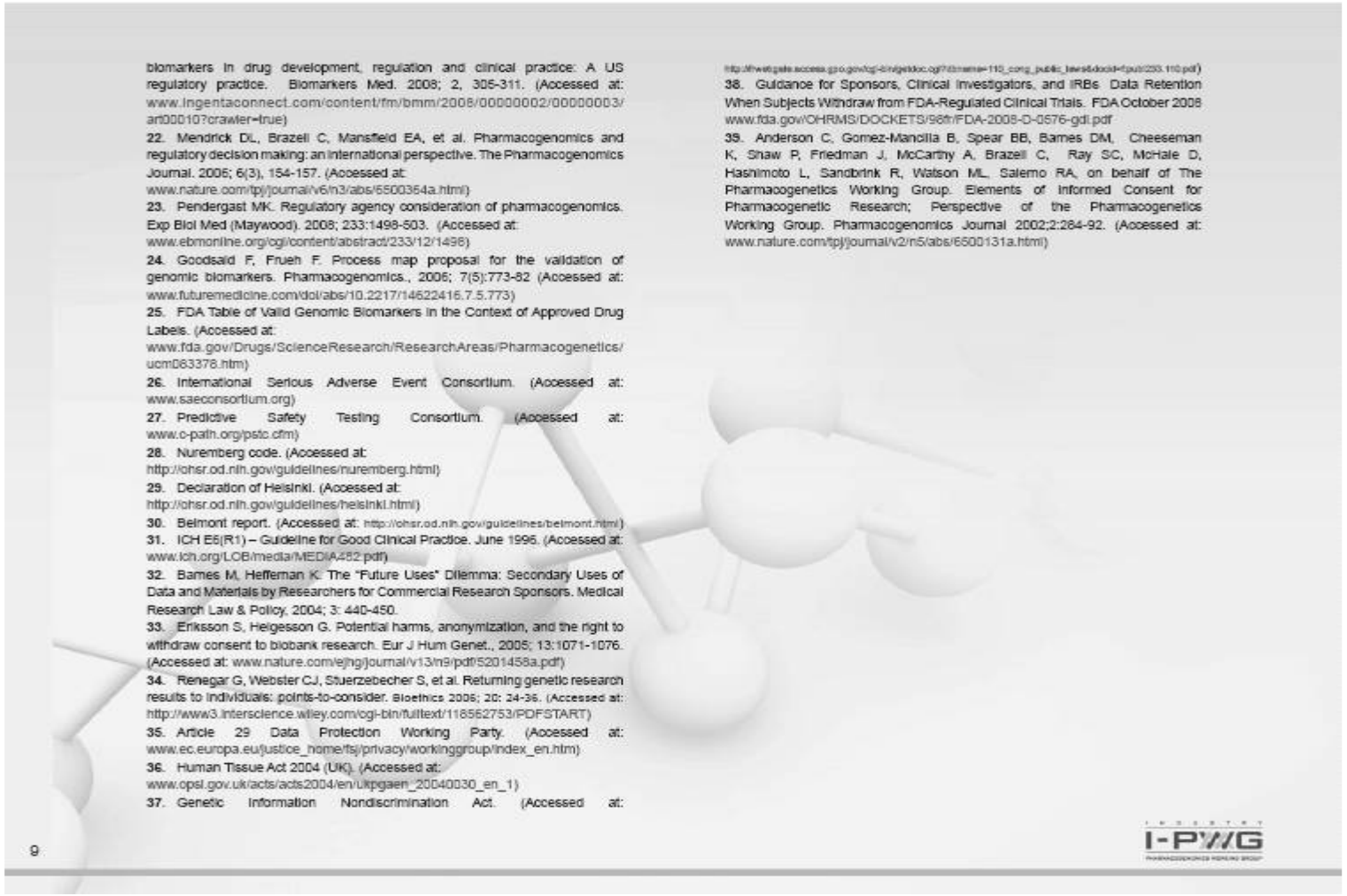

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12.4 Abbreviations

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
ASaT	All Subjects 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
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
DR	Drug Related
ECI	Events of Clinical Interest
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organisation for Research and Treatment of Cancer
ePRO	Electronic Patient Reported Outcomes

Abbreviation/Term	Definition
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
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

Abbreviation/Term	Definition
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
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
SOC	Standard of Care

Abbreviation/Term	Definition
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 selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; 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.

12.8 List of Strong CYP3A4 Inhibitors

For subjects receiving docetaxel, avoid using concomitant strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin and voriconazole) Taxotere (docetaxel) Prescribing Information, 12/2013.

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	