Official Protocol Title:	A Phase 3 Clinical Trial of Pembrolizumab (MK-3475) in First Line Treatment of Recurrent/Metastatic Head and Neck Squamous Cell Carcinoma
NCT number:	NCT02358031
Document Date:	11-Jan-2019

THIS PROTOCOL AMENDMENT AND ALL OF THE INFORMATION RELATING TO IT ARE CONFIDENTIAL AND PROPRIETARY PROPERTY OF MERCK SHARP & DOHME CORP., A SUBSIDIARY OF MERCK & CO., INC., WHITEHOUSE STATION, NJ, U.S.A.

SPONSOR:

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
(hereafter referred to as the Sponsor or Merck)
One Merck Drive
P.O. Box 100
Whitehouse Station, NJ 08889-0100, U.S.A.

Protocol-specific Sponsor Contact information can be found in the Investigator Trial File Binder (or equivalent).

TITLE:

A Phase 3 Clinical Trial of Pembrolizumab (MK-3475) in First Line Treatment of Recurrent/Metastatic Head and Neck Squamous Cell Carcinoma

IND NUMBER: 122,325
EudraCT NUMBER: 2014-003698-41

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Amendment 10/Global	11-Jan-2019	Modified to indicate the number of expected events, rather than required events, references to "event-driven" were removed, and text was modified to describe the timing of the final analysis to account for the scenario if the number of deaths for one hypothesis accumulates slower than expected to prevent the trial continuing for an unreasonable period for the final analysis.
Amendment 9/Global	09-Nov-2017	Dose modification guidelines were updated per health authority feedback. Hypotheses for PFS and OS superiority in biomarker positive subpopulation were added. Follow-up time was increased at the second interim analysis and final analysis to allow adequate follow-up time to assess long-term effects of pembrolizumab. Language was added to enable survival follow-up activities throughout the study at timepoints specified by the Sponsor.
Amendment 8/Global	24-Aug-2017	Follow-up time was increased at the interim and final analyses by 3 months to achieve data maturity at these timepoints.
Amendment 7/Global	17-Mar-2017	References to PD-L1 10% Combined Positive Score were removed; only the 20% and 1% cut points are planned to be analyzed.
Amendment 6/Sweden and Norway-specific amendment	16-Aug-2016	Updated to reflect changes in global amendment 5 and include information regarding benefit/risk assessment per country-specific requirements.

Document	Date of Issue	Overall Rationale
Amendment 5/Global	05-Aug-2016	OS was changed from a secondary objective to a primary objective, and biomarker population was updated to include PD-L1 ≥ 20% CPS, ≥ 10% CPS, ≥ 1% CPS. Sample size increased from 780 to 825 due to these changes. The strongly positive PD-L1 enrichment population was removed. Added QOL secondary objectives. Changed ORR, DOR, and PFS per irRECIST from secondary to exploratory objectives. Modified inclusion and exclusion criteria.
Amendment 4/Sweden and Norway-specific amendment	06-Aug-2015	Added information regarding benefit/risk assessment per country-specific requirements.
Amendment 3/Norway-specific amendment	31-Mar-2015	Added information regarding benefit/risk assessment and updated contraception language per country-specific requirements.
Amendment 2/Sweden-specific amendment	12-Mar-2015	Added information regarding benefit/risk assessment and updated contraception language per country-specific requirements.
Amendment 1/Global	26-Jun-2015	Sample size increased from 750 to 780 based on prevalence of strongly positive PD-L1 expression seen in data from the HNSCC cohorts in KEYNOTE-012. Added PFS hypothesis for pembrolizumab in combination with chemotherapy vs. standard treatment in subjects with strongly positive PD-L1 expression.
Original Protocol	05-Dec-2014	Not applicable.

SUMMARY OF CHANGES

PRIMARY REASON(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
8.1.3 8.1.4.2 8.2.7 8.2.9.2	Power and Sample Size Efficacy Interim Analyses Sample Size and Power Calculation Efficacy Interim Analyses	Edits were made to Table 17 and Table 23 to indicate the number of expected events, rather than required events. References to "event-driven" were removed. Text was modified to describe the timing of the final analysis to account for the scenario if the number of deaths for one hypothesis accumulates slower than expected.	To prevent the trial from continuing to an unreasonable duration for the final analysis.

ADDITIONAL CHANGE(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
2.1	Trial Design	Corrected language to indicate that interim PFS/OS analyses are time-driven, rather than event-driven.	Updated to be consistent with Section 8.
4.2.2	Rationale for Dose Selection/Regimen/Modification	Corrected the following text to indicate pembrolizumab dosing is Q3W: Five studies compared 2 mg/kg Q3W vs. 10 mg/kg ~~Q2W~~ **Q3W**	Updated to correct the dose frequency of the 10 mg/kg dose.
4.2.3.1.2	Secondary (Rationale for Endpoints)	Removed DOR from statement to indicate only ORR is a secondary endpoint.	Updated to be consistent with other sections of the protocol.
5.2.1.2.1	Dose Modification for Pembrolizumab, Table 4	Solid organ transplant rejection (SOTR) was deleted from Grade 3, All Other Immune-related AEs, as an event that requires discontinuation.	Text updated to align with current pembrolizumab standard protocol template.
6.2	Second Course Phase – Retreatment with Pembrolizumab	An arrow was added to the Survival Status row to indicate that it is assessed throughout treatment and follow-up during the study, to align with Section 6.1.1 and Section 6.1.2. Footnote c was added to this row.	Correction of typographical omission.

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
7.1.5.3.2	Follow-up Visits	Language was added to allow a less-frequent imaging schedule with Sponsor approval.	To allow flexibility in imaging frequency for subjects who stopped treatment with pembrolizumab due to CR or who completed the scheduled pembrolizumab treatment period, and to align with pembrolizumab program standards.
7.2.1	Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor	An error in the spelling of cetuximab was corrected.	Correction of typographical error.
7.2.3.2	Events of Clinical Interest	The list of ECIs for the trial was corrected to remove Item 3, additional adverse events.	Corrected to align with edits made in Amendment 09.
8.2.5.2	Statistical Methods for Safety Analyses	Table 21 was modified to eliminate Tier 1 from the analysis strategy description.	Deleted to align with edits made in sSAP since no Tier 1 events are in the trial.

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
8.2.9.2	Efficacy Interim Analyses	Table 23 was corrected. Under IA2 and Final Analysis sections of the table, "OS superiority mono/combo vs. SOC in subjects with PD-L1 CPS 20 (H10/H14)" was modified to read "OS superiority mono/combo vs. SOC in all subjects H10/H14)". Text was added to describe PFS analyses; the Lan and DeMets (1989) calendar time method will be used for alpha-spending to generate the group-sequential design. The updated bounds for the PFS hypotheses were added in Table 24.	Correction of an error in Amendment 09. This was added to the sSAP prior to IA1 to account for the scenario if events accumulate faster than expected.

1.0 TRIAL SUMMARY

Abbreviated Title	Pembrolizumab as First Line Treatment in Subjects with Recurrent/Metastatic HNSCC
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	(1) Pembrolizumab (MK-3475) 200 mg every 3 weeks (Q3W); or (2) Pembrolizumab (MK-3475) 200 mg Q3W + Platinum + 5-Fluorouracil (5-FU); or (3) Cetuximab 400 mg/m^2 initial dose followed by 250 mg/m^2 (weekly) + Platinum + 5-FU (Platinum is either Cisplatin 100 mg/m^2 Q3W or Carboplatin AUC 5 Q3W; 5-FU is 1000 mg/m^2/day continuous from Day 1 to Day 4 Q3W)
Number of trial subjects	Approximately 825 subjects will be enrolled.
Estimated duration of trial	The sponsor estimates that the trial will require approximately 60 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, drop out, or loss-to-follow-up from the time the subject signs the Informed Consent Form (ICF) through the final contact. After a screening phase of up to 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 AEs, intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw the subject, noncompliance with trial treatment or procedures requirements, subject receives 24 months of study medication (pembrolizumab arms only), pregnancy, or administrative reasons. Subjects on either pembrolizumab arm who attain a complete response (CR) 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 CR and stop trial treatment may be eligible for up to one year of retreatment upon experiencing centrally-verified disease progression. The decision to retreat will be at the discretion of the investigator only if the subject meets 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] and events of clinical interest [ECIs] will be collected for 90 days after the end of treatment). Subjects who discontinue for reasons other than centrally-verified disease progression will have post-treatment follow-up for disease status until disease progression is verified by the central imaging vendor, 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.

Randomization Ratio	1:1:1

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, or pembrolizumab plus platinum plus 5-FU chemotherapies versus platinum plus 5-FU plus cetuximab in subjects with advanced head and neck cancer to be conducted in conformance with Good Clinical Practices (GCP). Approximately 825 subjects with first line recurrent or metastatic (R/M) head and neck cancer will be enrolled for examination of the efficacy and safety of pembrolizumab versus pembrolizumab plus chemotherapy versus standard of care with cetuximab and chemotherapy. Subjects will be randomized 1:1:1 between the 3 arms of the trial.

The study will be stratified. Stratification factors are described in Section 5.4.

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 a group sequential design based on pre-specified criteria, using an independent, external Data Monitoring Committee (DMC) to monitor safety and efficacy. There will be 2 interim PFS/OS analyses, 1 final OS analysis, 1 planned interim safety analysis, and quarterly safety monitoring. The interim safety analysis will be conducted when 10 subjects in the pembrolizumab plus chemotherapy arm have completed 2 cycles of treatment. The interim PFS/OS analyses are time-driven. More details are given in Section 8.2.9.

Results of the interim analyses will be reviewed by the DMC, which will make recommendations to the Sponsor to continue, modify or end the trial according to the plan described briefly in Section 2.2 - Trial Diagram and in detail in Section 8.0 - Statistical Analysis Plan.

2.2 Trial Diagram

The trial design is depicted in Figure 1.

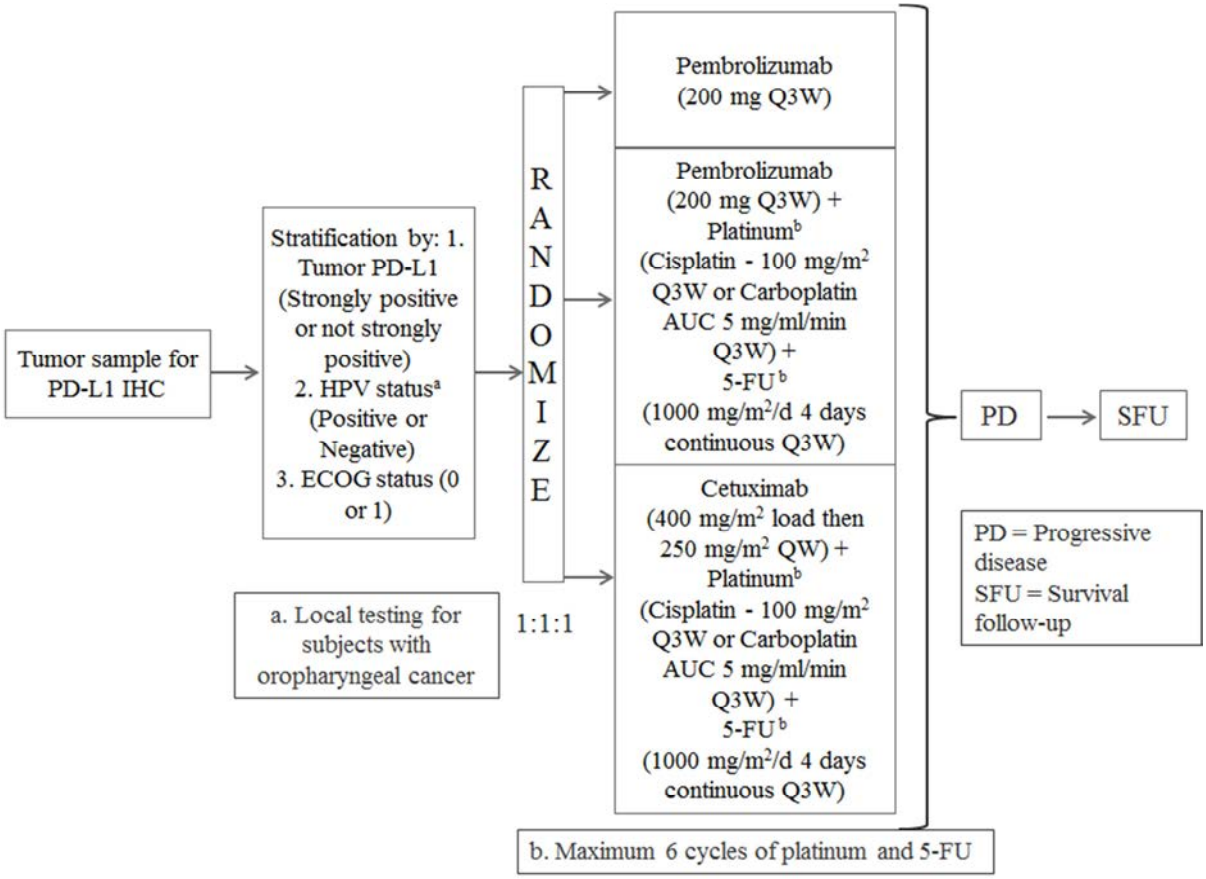


Figure 1 Trial Diagram

Choice of cisplatin or carboplatin will be made by the investigator before randomization.

3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

3.1 Primary Objective(s) & Hypothesis(es)

PD-L1 Positive Populations: subjects with programmed cell death ligand 1 (PD-L1) positive expression defined by ≥20 Combined Positive Score (CPS) and by ≥1 CPS; henceforth abbreviated as PD-L1 CPS 20 and PD-L1 CPS 1, respectively.

(1) **Objective:** To compare the Progression Free Survival (PFS) per RECIST 1.1 as assessed by blinded independent central review (BICR) in first line recurrent/metastatic (R/M) head and neck squamous cell carcinoma (HNSCC) subjects, treated with pembrolizumab monotherapy versus standard treatment.

Hypothesis (H1): Pembrolizumab monotherapy prolongs PFS by RECIST 1.1 (BICR) in a subgroup of first line R/M HNSCC subjects with PD-L1 CPS 20 compared to standard treatment.

Hypothesis (H2): Pembrolizumab monotherapy prolongs PFS by RECIST 1.1 (BICR) in a subgroup of first line R/M HNSCC subjects with PD-L1 CPS 1 compared to standard treatment.

Hypothesis (H3): Pembrolizumab monotherapy prolongs PFS by RECIST 1.1 (BICR) in all first line R/M HNSCC subjects compared to standard treatment.

(2) **Objective:** To compare PFS per RECIST 1.1 as assessed by BICR in first line R/M HNSCC subjects, treated with pembrolizumab in combination with chemotherapy versus standard treatment.

Hypothesis (H4): Pembrolizumab in combination with chemotherapy prolongs PFS by RECIST 1.1 (BICR) in a subgroup of first line R/M HNSCC subjects with PD-L1 CPS 20 compared to standard treatment.

Hypothesis (H5): Pembrolizumab in combination with chemotherapy prolongs PFS by RECIST 1.1 (BICR) in a subgroup of first line R/M HNSCC subjects with PD-L1 CPS 1 compared to standard treatment.

Hypothesis (H6): Pembrolizumab in combination with chemotherapy prolongs PFS by RECIST 1.1 (BICR) in all first line R/M HNSCC subjects compared to standard treatment.

(3) **Objective:** To evaluate the overall survival (OS) in first line R/M HNSCC subjects, treated with pembrolizumab monotherapy versus standard treatment.

Hypothesis (H7): Pembrolizumab monotherapy prolongs OS in first line R/M HNSCC subjects with PD-L1 CPS 20 compared to standard treatment.

Hypothesis (H8): Pembrolizumab monotherapy prolongs OS in first line R/M HNSCC subjects with PD-L1 CPS 1 compared to standard treatment.

Hypothesis (H9): Pembrolizumab monotherapy is non-inferior to standard treatment in terms of OS in all first line R/M HNSCC subjects.

Hypothesis (H10): Pembrolizumab monotherapy prolongs OS in all first line R/M HNSCC subjects compared to standard treatment.

(4) **Objective:** To evaluate OS in first line R/M HNSCC subjects, treated with pembrolizumab in combination with chemotherapy versus standard treatment.

Hypothesis (H11): Pembrolizumab in combination with chemotherapy prolongs OS in first line R/M HNSCC subjects with PD-L1 CPS 20 compared to standard treatment.

Hypothesis (H12): Pembrolizumab in combination with chemotherapy prolongs OS in first line R/M HNSCC subjects with PD-L1 CPS 1 compared to standard treatment.

Hypothesis (H13): Pembrolizumab in combination with chemotherapy is non-inferior to standard treatment in terms of OS in all first line R/M HNSCC subjects.

Hypothesis (H14): Pembrolizumab in combination with chemotherapy prolongs OS in all first line R/M HNSCC subjects compared to standard treatment.

The statistical criterion for the success of H9 and H13 is that, if the upper bound of the confidence interval, based on the alpha level allocated to the analysis, for the hazard ratio is <1.2, then pembrolizumab experimental arm could be considered as non-inferior to the standard treatment arm in terms of OS.

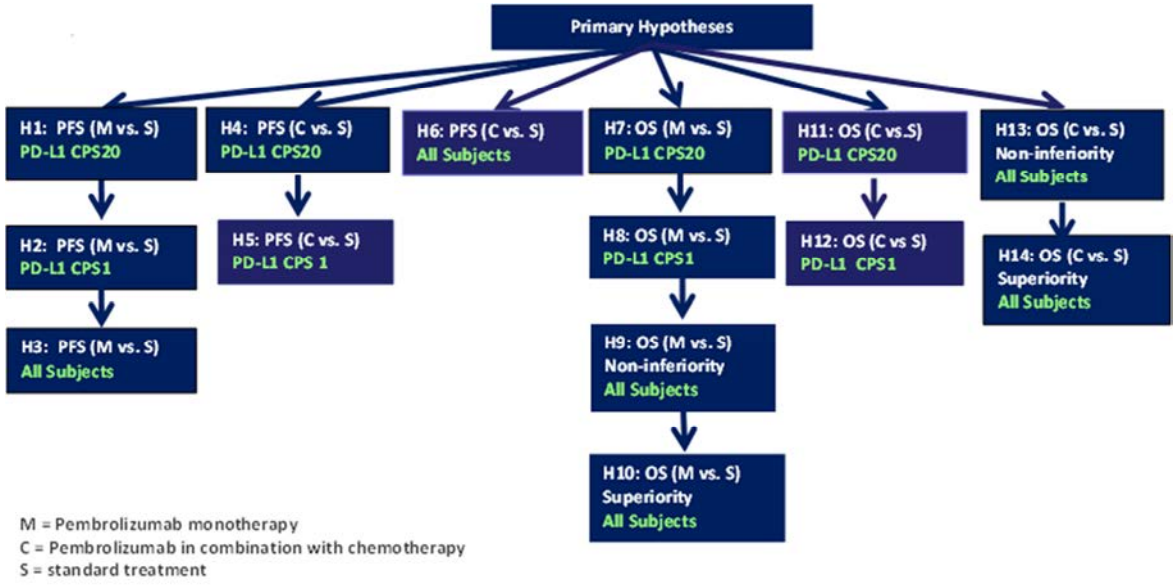


Figure 2 Primary Hypotheses Schematic (Except for H9 and H13, all the other hypotheses are tested for superiority)

3.2 Secondary Objective(s) & Hypothesis(es)

(1) **Objective**: To evaluate the safety and tolerability profile of pembrolizumab monotherapy or a combination of pembrolizumab with chemotherapy in all first line R/M HNSCC subjects.

The following secondary objectives will be evaluated in (1) PD-L1 CPS 20, (2) PD-L1 CPS 1 and (3) all subjects for both pembrolizumab in combination with chemotherapy and pembrolizumab monotherapy compared to standard treatment.

(2) **Objective**: To evaluate proportion progression-free at 6 months and 12 months per RECIST 1.1 by BICR of first line R/M HNSCC subjects.

(3) **Objective**: To evaluate objective response rate (ORR) per RECIST 1.1 by BICR in first line R/M HNSCC subjects.

(4) **Objective:** To evaluate mean change from baseline in global health status/quality of life in first line R/M HNSCC subjects.

(5) **Objective:** To evaluate time to deterioration (TTD) in global health status/quality of life, pain and swallowing in first line R/M HNSCC subjects.

3.2.1 Exploratory Objectives

1) **Objective:** To evaluate duration of response (DOR) per RECIST 1.1 by BICR in first line R/M HNSCC subjects.
2) **Objective:** To evaluate ORR, DOR and PFS using immune-related RECIST (irRECIST) as assessed by BICR in first line R/M HNSCC subjects.
3) **Objective:** To evaluate changes in health-related quality-of-life assessments from baseline in subjects with R/M HNSCC using the EORTC QLQ-C30 and EORTC QLQ-H&N35.
4) **Objective:** To characterize utilities in subjects with R/M HNSCC cancer using the EuroQol EQ-5D.
5) **Objective:** To evaluate changes in opioid analgesic use from baseline in subjects with R/M HNSCC, based on reported concomitant medications, supplemented with a daily Pain Medication Log.
6) **Objective**: To investigate the relationship between pembrolizumab treatment and biomarkers predicting response (e.g., PD-L1, genetic variation, serum soluble PD-L1) utilizing archival tumor tissue and blood sampling.
7) **Objective:** To explore the relationship between genetic variation and response to the treatment(s) administered. Variation across the human genome will be analyzed for association with clinical data collected in this study.

4.0 BACKGROUND & RATIONALE

4.1 Background

Pembrolizumab is a potent humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) with high specificity of binding to the programmed cell death 1 (PD-1) receptor, thus inhibiting its interaction with 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.

[redacted]

4.1.1 Pharmaceutical and Therapeutic Background

Pembrolizumab (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 Cytotoxic T-Lymphocyte-Associated Antigen-4 (CTLA-4) which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) [7; 8]. The structure of murine PD-1 has been resolved [9]. PD-1 and family members are type I transmembrane glycoproteins containing an Ig Variable-type (V-type) domain responsible for ligand binding and a cytoplasmic tail which is responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif (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 [13; 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 [13]. Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. PD-1 has been suggested to regulate tumor-specific T-cell expansion in subjects with melanoma (MEL) [21]. This suggests that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention.

4.1.2 Pre-clinical and Clinical Trials

Therapeutic studies in mouse models have shown that administration of antibodies blocking PD-1/PD-L1 interaction enhances infiltration of tumor-specific CD8+ T-cells and leads ultimately to tumor rejection, either as a mono-therapy or in combination with other treatment modalities. Anti-mouse PD-1 or anti-mouse PD-L1 antibodies have demonstrated anti-tumor responses as a mono-therapy in multiple 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; 28]. 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 (NSCLC), a number of advanced solid tumor indications (including head and neck cancer) 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 1b study of pembrolizumab in 4 indications, one of which includes patients with human papillomavirus (HPV)-negative and HPV-positive head and neck cancer. This trial enrolled 2 HNSCC cohorts (Cohorts B and B2) for a total 192 subjects with recurrent and/or metastatic squamous cell carcinoma of the head and neck for treatment with single agent pembrolizumab.

The pooled data from Cohorts B and B2 were presented at ASCO 2016 and described efficacy and safety results after long term follow-up [29]. Among the 192 subjects with R/M HNSCC that were enrolled, 60 subjects in Cohort B were treated at 10 mg/kg every 2 weeks

(Q2W) and 132 subjects in Cohort B2 were treated at 200 mg Q3W. The last subject was enrolled on 08-Oct-2014 and 32 (17%) subjects were still on treatment as of the 01-Sep-2015 data cutoff. Median age was 60 years; 83% of subjects were male; 70% had ECOG PS 1; and 61% had received ≥2 therapies for recurrent disease. ORR (confirmed) was 17.7% (95% CI, 12.6%-23.9%; 7 CRs, 27 PRs). Median follow-up duration in responders was 12.5 months (range, 8.4-24.4). As of the data cutoff, median DOR was not yet reached (range, 1.8+ to 21.8+ months) and responses were ongoing in 22 (76%) subjects. Responses of ≥6 months and ≥12 months were noted in 25 subjects and 4 subjects, respectively. Thirty-three (17%) subjects achieved stable disease. ORR was 21.9% (95% CI, 12.5%-34.0%) in HPV-positive subjects and 15.9% (95% CI, 10.0%-23.4%) in HPV-negative subjects. Median OS was 8.5 months (95% CI, 6.5-10.5), compared to the historical OS rate of 6 months for patients who progress following first line treatment [30]. The 6-month PFS rate was 24.9%. Treatment-related AEs (TRAEs) occurred in 122 (64%) subjects, and 23 (12%) subjects had a Grade 3-4 TRAE. No subjects died due to a TRAE. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) increases were the only Grade 3-4 TRAEs observed in >2 subjects.

KEYNOTE-055 is a Phase 2 study of single agent pembrolizumab (200 mg Q3W) in subjects with R/M HNSCC who progressed following treatment with platinum and cetuximab. Preliminary results from KEYNOTE-055 were presented at ASCO 2016 [31]. A total of 172 subjects were enrolled for safety, efficacy, and biomarker analyses. Preliminary analyses focused on the first 50 subjects enrolled. Median age was 59 years; 80% of subjects were male; and 84% had ≥2 prior lines of therapy for metastatic disease. Median follow-up time at the time of the data cutoff was 6.8 months (range, 0-12.1). Thirty-five (70%) subjects experienced a TRAE, with 6 (12.0%) subjects experiencing a Grade 3-5 TRAE. Two (4%) subjects discontinued and 1 (2%) subject died due to a TRAE. AEs of special immunologic interest occurred in 11 (22%) subjects; hypothyroidism (n = 7; all Grade 2) and pneumonitis (n = 2, Grade 2; n = 1, Grade 5) were the most common. Nine subjects had a confirmed partial response (PR) for an ORR of 18.0% (95% CI 8.6-31.4). Five subjects had ongoing responses at the data cutoff. The stable disease rate was 18.0% (n = 9; 95% CI 8.6-31.4).

Preliminary biomarker results from KEYNOTE-012 showed that when tumor and inflammatory cells were used to score PD-L1 status, an increase in ORR was observed between PD-L1+ versus PD-L1- tumors (P = 0.023); when scoring was restricted to tumor cells only, this increase was not seen. Improved PFS (P = 0.026) and OS (P = 0.008) were also observed in PD-L1+ versus PD-L1- tumors when scoring was conducted in tumor and inflammatory cells, but not tumor cells alone. In summary, inclusion of both tumor cells and inflammatory cells in immunohistochemistry (IHC) scoring (combined positive scoring, CPS) improves the ability to predict response based on PD-L1 status compared to tumor cells alone (tumor proportion scoring, TPS) in subjects with R/M HNSCC. In addition, preliminary results from KEYNOTE-055 showed that using CPS 1 and 20 cutpoint demonstrates a positive predictive value (PPV) of [redacted]. The prevalence for CPS 1 and CPS 20 cutpoints are approximately 80% and 50%, respectively.

KEYNOTE-040 is a Phase 3, multicenter, international, randomized, open label trial of single agent pembrolizumab (200 mg Q3W) versus standard of care in subjects with R/M HNSCC. Results from KEYNOTE-040 showed that pembrolizumab demonstrated a greater benefit in subjects with PD-L1 expressing tumors. In the CPS 1 population, ORR was 17.3% for the pembrolizumab arm compared to 9.9% for the standard of care arm (CI: 0.6%-14.6%). The median OS is 8.7 months for the pembrolizumab arm compared to 7.1 months for the standard of care arm (HR=0.75, CI: 0.59-0.95) [61].

Based on the evolving information obtained from further analysis of the KEYNOTE-012 study as well as emerging biomarker data from KEYNOTE-055, we plan to evaluate PD-L1 expression using a CPS 20 cutpoint, which balances all factors including PPV, prevalence, the biomarker specificity/sensitivity, in addition to the 50% TPS previously specified. The CPS 1 cutpoint will also be evaluated. 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, KEYNOTE-055, and KEYNOTE-040 clinical trials as the Sponsor remains blinded to the ongoing KEYNOTE-048 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

A variety of chemotherapies are used for patients with R/M, first line HNSCC. Early studies demonstrated small survival benefits after treatment with cisplatin or methotrexate or chemotherapy combinations [33]. In the 18 years following this early report from the Liverpool consortium, cisplatin, carboplatin, methotrexate, paclitaxel, 5-fluorouracil (5-FU), and their various combinations have been evaluated in several Phase 3 trials [34; 35; 36; 37; 38; 39]. The combination of cisplatin and 5-FU showed generally better results than other regimens with overall response rates ranging from 11 to 37% and OS ranging from 23 to 36 weeks. No Phase 3 randomized trial showed a significant advantage in OS for any regimen until cetuximab in combination with platinum and 5-FU was compared with platinum and 5-FU in the EXTREME trial. Addition of cetuximab to cisplatin-5-FU demonstrated the first significant increase in OS in first line head and neck cancer in EXTREME [40]. Overall survival was increased from 30 weeks for platinum-5-FU to 40 weeks with the platinum/5-FU/cetuximab regimen. In EXTREME, the corresponding ORR increased from 20 to 30% and the PFS increased from 13 to 22 weeks. The EXTREME regimen is associated with an 82% frequency of grade 3/4 toxicities. Paclitaxel or docetaxel-based regimens are used by many clinicians, but taxane-containing regimens have yet to be directly compared with the EXTREME regimen in a randomized Phase 3 trial. Recent literature showed that the median OS of the EXTREME regimen may be prolonged (approximately 11 months) compared with original median OS published in 2008 (approximately 10 months) [58, 59, 60].

Since R/M first line patients have somewhat heterogeneous characteristics, National Comprehensive Cancer Network (NCCN) guidelines generally highlight the importance of considering individualized systemic therapies based on patient characteristics, given the toxicity of the EXTREME regimen. The only Category 1 evidence-supported combination

regimen recommended by NCCN is the EXTREME regimen. NCCN guidelines offer consideration of the use of alternative combination regimens including platinum plus taxane, cisplatin plus cetuximab and cisplatin plus 5-FU, or the use of these agents as monotherapies.

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 [41], and accounts for 5% of all malignancies [42]. Although the head and neck region contains a wide diversity of structures and cell types, the vast majority of head and neck cancers arise from the mucosa of the upper aerodigestive tract and are predominantly squamous cell in origin.

A large number of patients with head and neck cancer initially present with locally advanced, Stage III/IV disease that is initially treated with combinations of chemotherapy, radiation and/or surgery. This initial treatment is generally designated as "definitive" therapy, which typically combines chemoradiation and surgery and can result in disease control rates ranging between 33 and 86% of patients. Patients who progress after initial definitive therapy require subsequent treatment for recurrent (R) disease. Patients who initially present with metastatic (M) disease generally receive the same therapy as those with recurrent disease after definitive treatment. Together, patients with recurrent or metastatic (R/M) disease receive the first line chemotherapies outlined above (Section 4.1.4).

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 [43]. 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. Investigator site assessment of HPV using IHC staining for the p16 protein will be used for the subjects with oropharyngeal cancer prior to randomization.

4.2.2 Rationale for Dose Selection/Regimen/Modification

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

- Clinical data from eight randomized studies demonstrating flat dose- and exposure- efficacy relationships from 2 mg/kg Q3W to 10 mg/kg every two weeks (Q2W)
- Clinical data showing meaningful improvement in benefit-risk including overall survival at 200 mg Q3W across multiple indications
- Pharmacology data showing full target saturation in both systemic circulation (inferred from pharmacokinetic [PK] data) and tumor (inferred from physiologically based pharmacokinetic [PBPK] analysis) at 200 mg Q3W

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

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

Finally, population PK analysis of pembrolizumab, which characterized the influence of body weight and other subject covariates on exposure, has shown that the fixed-dosing provides similar control of PK variability as weight based dosing, with considerable overlap in the distribution of exposures from the 200 mg Q3W fixed dose and 2 mg/kg Q3W dose. Supported by these PK characteristics, and given that fixed-dose has advantages of reduced dosing complexity and reduced potential of dosing errors, the 200 mg Q3W fixed-dose was selected for evaluation across all pembrolizumab protocols.

4.2.2.1 Rationale for the Use of Comparator/Placebo

See Section 4.1.4.

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 efficacy of antineoplastic therapy. Achieving superiority in overall survival, however, is likely to be limited by dilution of benefit with multiple post-progression therapies as well as disproportionate crossover in the control arm to available PD-1/PD-L1 axis of therapies. Therefore, overall survival of pembrolizumab treatment is evaluated as non-inferior before superior to standard of care treatment in the analysis. In addition, pembrolizumab monotherapy has shown OS benefit in previously treated HNSCC patient population (Section 4.1.3).

Progression-free survival is an acceptable measure of clinical benefit for a randomized Phase 3 trial that demonstrates superiority of a new antineoplastic therapy, especially if the magnitude of effect is large and the therapy has a favorable risk-benefit profile. The substantial toxicity of the EXTREME regimen contributes to a comparative lack of acceptance by patients and physicians, arguing for a critical need to establish an effective alternative regimen. The available trials of PD-1/PD-L1 therapies in later lines of therapy as well as their potential approval in previously treated patients will lead to substantial crossover of patients receiving the EXTREME comparator for the duration of this trial. Taken together, these factors support the use of PFS as a co-primary endpoint in this trial.

RECIST 1.1 will be used to determine the dates of progression as this methodology is accepted by regulatory authorities. Because the treatment assignment is unblinded, images will be read by independent radiologists blinded to treatment assignment to minimize bias in the response assessments. In addition, final determination of radiologic progression will be based on the central assessment of progression, rather than site assessment. Real-time determination of radiologic progression as determined by central review will be communicated to the site.

4.2.3.1.2 Secondary

ORR by RECIST 1.1 criteria as assessed by blinded independent central radiology review will serve as an additional measure of efficacy.

4.2.3.2 Immune-related RECIST

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

If radiologic imaging by central imaging vendor verifies initial PD, tumor assessment should be repeated ≥4 weeks later in order to confirm PD with the option of continuing treatment per below while awaiting radiologic confirmation of progression. If repeat imaging shows a reduction in the tumor burden compared to the initial scan demonstrating PD, treatment may be continued / resumed. If repeat imaging confirms PD, subjects will be discontinued from study therapy (exception noted in Section 7.1.2.6.3). In determining whether or not the tumor burden has increased or decreased, investigators should consider all target lesions as well as non-target lesions (please refer to the Site Imaging Manual).

In subjects who have initial evidence of radiological PD verified by central imaging vendor, 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 pembrolizumab treatment while waiting for confirmation of PD if they are clinically stable as defined by the following criteria:

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

When feasible, subjects should not be discontinued until progression is confirmed. This allowance to continue treatment despite initial radiologic progression takes into account the observation that some subjects can have a transient tumor flare in the first few months after the start of immunotherapy, but with subsequent disease response. Subjects that are deemed clinically unstable are not required to have repeat imaging for confirmation of PD.

Subjects randomized to the standard treatment arm will not have irRECIST assessments.

4.2.3.3 Rationale for Prospective Stratification and Evaluation of Biomarker Subpopulation

Late line R/M HNSCC subjects evaluated in KEYNOTE-012 were enrolled if their tumor PD-L1 immunohistochemistry (IHC) showed any evidence of ligand expression. KEYNOTE-012 sought to evaluate responses in a population of subjects likely to demonstrate higher ORRs than anticipated for subjects with PD-L1 negative tumors. Studies to date in additional indications (melanoma and lung) suggest that subjects may respond to pembrolizumab even if their tumors show little or no PD-L1 by IHC, although potentially at a lower rate of response. KEYNOTE-012 was amended to include subjects that are both positive and negative by IHC, and response rates are being determined and evaluated for various expression levels of PD-L1.

Data from epidemiology studies suggest that PD-L1 expression in a subject's tumor(s) varies with the circumstances of testing. Overall, the evaluation of tumor PD-L1 status likely most accurately reflects expression in the tumor to be treated using tumor biopsies nearest the time of treatment initiation, and at times after any previous cancer therapies were administered. Consequently, subjects enrolled in KEYNOTE-048 will preferably have a biopsy of their tumor evaluated either using initial diagnostic specimens or from newly obtained biopsies if subjects received cancer treatment after their diagnostic biopsy. IHC will be used to evaluate the PD-L1 status of the tumor specimen. Further details of the statistical approach to evaluating this population are described in Section 8.2.

4.2.3.4 Safety

The primary safety objective of this trial is to characterize the safety and tolerability of pembrolizumab in subjects with R/M HNSCC. The primary safety analysis will be based on subjects who experienced toxicities as defined by Common Toxicity Criteria for Adverse Events (CTCAE) criteria. Safety will be assessed by quantifying the toxicities and grades experienced by subjects who have received pembrolizumab, including serious adverse events (SAEs) and events of clinical interest (ECIs). Safety will be assessed by reported adverse experiences using CTCAE, Version 4.0. The attribution to drug, time-of-onset, duration of the event, its resolution, and any concomitant medications administered will be recorded. AEs will be analyzed including but not limited to all AEs, SAEs, fatal AEs, and laboratory changes. Furthermore, specific immune-related adverse events (irAEs) will be collected and designated as immune-related events of clinical interest (ECIs) as described in Section 7.2.3.2. 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-neoplastic 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-neoplastic therapy, whichever occurs first. SAEs and ECIs that occur within 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, should be followed and recorded.

4.2.3.5 Patient Reported Outcomes

The EORTC QLQ-C30, EORTC QLQ-H&N35 and EQ-5D are not pure efficacy or safety endpoints because they are affected by both disease progression and treatment tolerability. A Pain Medication Log will collect information on daily prescription medication use, which may indicate changes in pain either affected by disease progression and/or treatment tolerability.

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

The EORTC QLQ-C30 is the most widely used cancer specific health-related Quality of Life (HRQoL) instrument, which contains 30 items and measures 5 functional dimensions (physical, role, emotional, cognitive and social), 3 symptom items (fatigue, nausea/vomiting, and pain), 6 single items (dyspnea, sleep disturbance, appetite loss, constipation, diarrhea, and financial impact), and a global health and quality of life scale [44].

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 [45; 46] 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 [47]. 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 R/M HNSCC, which led to the FDA approval of cetuximab monotherapy in subjects with recurrent or metastatic SCCHN refractory to cisplatin [48; 49]. 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 [46].

For the global health status/quality of life and function scales, a higher value indicates a better level of function; for symptom scales and items, a higher value indicates increased severity of symptoms. Prior literature indicates that head and neck pain and the ability to swallow are clinically relevant symptom measures in the R/M HNSCC population [48; 49; 50; 51]. Thus, time to deterioration (TTD) in the pain and swallowing multi-item scales of the EORTC QLQ-H&N35, in addition to TTD and mean change from baseline in global health status/quality of life scale of the EORTC QLQ-C30, will be evaluated as secondary objectives.

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.

4.2.3.5.2 eEuroQuol EQ-5D

The electronic EuroQol-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 quality adjusted life-years (QALYs). The 5 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 3-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 electronic EORTC QLQ-C30 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.

4.2.3.5.3 Pain Medication Log

The Pain Medication Log is a paper-based pamphlet that will be completed daily by subjects to document the use of prescription pain medications. The objective of the Pain Medication Log is to provide data to assess changes in opioid analgesic use from baseline. The Pain Medication Log will record the use of prescription pain medication by the subject, the name of each pain medication, and the dose of each tablet taken or patch used. For each prescription pain medication tablet, subjects will indicate number of tablets taken. For each prescription pain medication patch, subjects will indicate the days the patch was used.

It is recommended that subjects complete the log starting from the Screening Visit. The Pain Medication Log is to be completed by subjects daily and submitted to site personnel at each scheduled visit as specified in the study Flow Chart, beginning with Screening until 30 days post-treatment discontinuation. At each study visit, study personnel will verify the

information with the subject. Site personnel will determine the use and the total daily dose of prescription pain medication(s) and enter these data on the concomitant medication form of the case report form (CRF).

4.2.3.6 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

PD-L1 expression in tumor tissue will be characterized by immunohistochemistry to explore the relationship between tumor PD-L1 expression and response to treatment with pembrolizumab. Other biomarkers contributing to the PD-1/PD-L1 axis 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 attempt to define a gene set critical for clinical response to pembrolizumab. The hypothesis to be tested is that pembrolizumab induces responses in tumors that reflect an inflamed/ immune phenotype based on gene expression signatures capturing PD-L1 and interferon-gamma transcriptional programs. Global profiling will also be pursued. Expression of individual genes related to the immune system may also be evaluated such as immune signatures and critical cytokines (e.g., IL-10). MicroRNA profiling may also be pursued in serum samples.

Proteomic Analysis

In addition to expression on the tumor tissue, PD-L1 can be shed from tumor and released into the blood. Enzyme-linked immunoassay can measure PD-L1 in serum and correlate this expression with response to pembrolizumab therapy, as well as levels of PD-L1 IHC or protein in the tumor. Blood would be a less invasive 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.

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 AEs, the data might inform optimal use of therapies in the patient population. This research contributes to understanding genetic determinants of efficacy and safety associated with the treatments in this study.

4.2.3.7 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.

4.3 Benefit/Risk

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

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

Pembrolizumab has a positive benefit-risk profile and is well tolerated in the approved indications. Publications of a significantly positive benefit/risk ratio have been reported for melanoma in a single arm study encompassing nearly 1000 patients (KEYNOTE-001), which led to US FDA approval in September 2014. Pembrolizumab has subsequently received approval for the treatment of patients with non-small cell lung cancer (NSCLC) and for the treatment of patients with recurrent or metastatic head and neck squamous cell carcinoma (HNSCC). The Investigator Brochure provides additional details about these approvals. The US FDA approval to treat patients with R/M HNSCC with disease progression on or after platinum-containing chemotherapy was based on the favorable tumor response rate and durability of responses seen in KEYNOTE-012 and KEYNOTE-055. The potential benefits for patients with HNSCC are addressed in Section 4.1.3, which details responses of subjects with HNSCC in KEYNOTE-012 and KEYNOTE-055.

The most common pembrolizumab adverse reactions (reported in ≥20% of patients) include pruritus, diarrhea, and cough. In the pembrolizumab monotherapy trials, the incidence of Grade 3-5 drug-related AEs across studies is 13.8%. Pembrolizumab immune-mediated Adverse Events of Special Interest (AEOSIs) are relatively uncommon. The most frequently reported AEOSI is hypothyroidism, with an overall incidence of 8.5%. Furthermore, most AEOSIs are mild to moderate in severity, and are generally readily manageable with appropriate care in the clinical setting. The adverse events associated with pembrolizumab are milder and less frequent than events reported for the cetuximab, platinum, 5-FU comparator in this trial. For the cetuximab-platinum-5-FU comparator, Grade 4 events are seen in 31% of patients, including neutropenia as the most frequent Grade 4 event (4%). For the cetuximab-platinum-5FU arm, 82% of patients experienced a Grade 3 or 4 AE including 22% with neutropenia, 13% with anemia and 11 % with thrombocytopenia.

The safety profile of the KEYNOTE-048 pembrolizumab combination arm (pembrolizumab plus platinum plus 5-FU), together with the pembrolizumab monotherapy arm and standard treatment arm (cetuximab plus chemotherapy) has been evaluated by an external DMC at an early interim safety analysis in the initial stage of this trial, and continues to be evaluated on a quarterly basis. Following DMC review of the unblinded safety data (including the recent DMC meeting in February 2017), the DMC recommended to continue the trial with no changes.

The durability of immunotherapeutic responses, together with the tolerability advantage of pembrolizumab argues strongly for a direct comparison of the current approved cetuximab-platinum-5-FU regimen both with pembrolizumab monotherapy and with a pembrolizumab-platinum-5-FU combination as proposed in this trial. As noted, this clinical trial is designed to provide a direct comparison between the current regimen and the investigational arms proposed in this trial.

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

Male and 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.

5.1.2 Subject Inclusion Criteria

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

1. Have histologically or cytologically-confirmed R/M HNSCC that is considered incurable by local therapies.
    - Subjects should not have had prior systemic therapy administered in the recurrent or metastatic setting. Systemic therapy which was completed more than 6 months prior to signing consent if given as part of multimodal treatment for locally advanced disease is allowed.
    - The eligible primary tumor locations are oropharynx, oral cavity, hypopharynx, and larynx.
    - Subjects may not have a primary tumor site of nasopharynx (any histology).
2. Be willing and able to provide written informed consent for the trial. The subject may also provide consent for Future Biomedical Research. However, the subject may participate in the main trial without participating in Future Biomedical Research.
3. Be ≥ 18 years of age on day of signing informed consent.
4. Have 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.
5. Have a performance status of 0 or 1 on the ECOG Performance Scale.
6. 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/μL (1.5 x 10^9/L)
Platelets	≥100,000/μL (100 x 10^9/L)
Hemoglobin	≥9 g/dL (90 g/L) or ≥5.6 mmol/L
Renal	
Creatinine **OR** Measured or calculated[a] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5xULN **OR** ≥60 mL/min for subject with creatinine levels >1.5x institutional ULN
Hepatic	
Total bilirubin	≤1.5xULN **OR** Direct bilirubin ≤ULN for subjects with total bilirubin levels >1.5xULN
AST (SGOT) and ALT (SGPT)	≤2.5xULN **OR** ≤5xULN for subjects with liver metastases
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT)	≤1.5xULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
Activated Partial Thromboplastin Time (aPTT) or Partial Thromboplastin Time PTT[b]	≤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. [b] PTT may be performed if the local lab is unable to perform aPTT.	

7. Have results from testing of HPV status for oropharyngeal cancer defined as p16 IHC testing using CINtec® p16 Histology assay and a 70% cutoff point (please see Section 7.1.2.7 for details). If HPV status was previously tested using this method, no additional testing is required.

   Note: Tumor p16 expression must be evaluated by assessment of IHC analysis with CINtec® p16 Histology assay (Ventana Medical Systems Inc., Tucson AZ) using 'Benchmark Ultra' autostainer (Ventana, Tucson, AZ) 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: HPV stratification in this trial will be performed using local testing of HPV status in patients with oropharynx cancer using the specified method.

   Note: If local p16 testing results are not available, or cannot be assessed by the specified method, a tumor tissue sample may be submitted for p16 testing at the designated central laboratory.

   Note: Oral cavity, hypopharynx, and larynx cancer are not required to undergo HPV testing by p16 IHC as by convention these tumor locations are assumed to be HPV negative.

8. Have provided tissue for PD-L1 biomarker analysis from a core or excisional biopsy (fine needle aspirate [FNA] is not adequate). Repeat samples may be required if adequate tissue is not provided. A newly obtained biopsy (within 90 days prior to start of study treatment) is strongly preferred, but an archival sample is acceptable.

   Note: Refer to Section 7.1.2.7 for more information on tissue sample requirements.

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

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

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

11. Male subjects should agree to use an adequate method of contraception starting with the first dose of study therapy through 180 days after the last dose of study therapy.

    Note: Abstinence is acceptable if this is the usual lifestyle and preferred method of 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. Has progressive disease (PD) within six (6) months of completion of curatively intended systemic treatment for locoregionally advanced HNSCC.
3. Has had radiation therapy (or other non-systemic therapy) within 2 weeks prior to randomization or subject has not fully recovered (i.e., ≤Grade 1 or at baseline) from adverse events due to a previously administered treatment.

   Note: Subjects with ≤Grade 2 neuropathy, ≤Grade 2 alopecia, or laboratory values on Table 1 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.

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

   Note: Participation in the follow-up phase (receiving no study treatment) of a prior study is allowed.

5. Has a life expectancy of less than 3 months and/or has rapidly progressing disease (e.g. tumor bleeding, uncontrolled tumor pain) in the opinion of the treating investigator.
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. Corticosteroid use as pre-medication for allergic reactions (e.g. IV contrast), or as a prophylactic management of adverse events related to the chemotherapies specified in the protocol is allowed. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.
7. 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, curatively resected *in situ* cervical cancer, and curatively resected *in situ* breast cancer. Other exceptions may be considered with Sponsor consultation.

   Note: The time requirement for no malignancy for 5 years does not apply to the cancer for which a subject is enrolled in the trial.
8. Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis.

   Note: Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging (using the identical imaging modality for each assessment, either MRI or CT scan) for at least 4 weeks prior to the first dose of trial treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to trial treatment. This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability.
9. Active autoimmune disease that has required systemic treatment in past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.
10. Has had an allogeneic tissue/solid organ transplant.
11. Has a history of (non-infectious) pneumonitis that required steroids or current pneumonitis.
12. Has an active infection requiring systemic therapy.
13. 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.
14. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.

15. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the screening visit through 180 days after the last dose of trial treatment.

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

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

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

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

5.2 Trial Treatment(s)

The treatment(s) to be used in this trial are outlined below in Table 2.

Table 2 Trial Treatment

Drug	Dose/ Potency	Dose Frequency	Route of Administration	Regimen	Use
Pembrolizumab	200 mg	Every 3 weeks	Intravenous	Day 1 of each cycle (3 week cycles)	Experimental
Cisplatin	100 mg/m^2	Every 3 weeks	Intravenous	Day 1 of each cycle (3 week cycles) for 6 cycles	Comparator regimen and combination agent
Carboplatin	AUC 5	Every 3 weeks	Intravenous	Day 1 of each cycle (3 week cycles) for 6 cycles	Comparator regimen and combination agent
5-FU	1000 mg/m^2/day continuous from day 1-4 of each cycle	Every 3 weeks	Intravenous	Day 1 of each cycle (3 week cycles) for 6 cycles	Comparator regimen and combination agent
Cetuximab	Initial dose on day 1 is 400 mg/m^2 over 2 hours followed by weekly doses of 250 mg/m^2 over 1 hour.	Every week	Intravenous	Days 1, 8, and 15 of each cycle (3 week cycles)	Comparator regimen

Subjects may receive a maximum of 6 cycles (infusions) of platinum and 5-FU

Trial treatment should begin on the day of randomization or within 5 days of the date on which the subject is allocated/assigned.

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

For any commercially available product that is provided by the trial site, subsidiary or designee every attempt will be made to source these supplies from a single lot/batch number. The trial site 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.

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

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 m2 should be calculated per local guidance.

Carboplatin will be administered at an AUC/time curve of 5 mg/mL/min as an IV infusion on Cycle Day 1 of a 3-week cycle. Pursuant to the CTEP Information Letter Regarding the AUC Based Dosing of Carboplatin, the maximum carboplatin dose should not exceed the target AUC (mg*min/mL)*150 mL/min, but it may be less. As well, the glomerular filtration rate (GFR) used in the Calvert formula to AUC-based dosing should not exceed 125 mL/min. For this trial, the maximum dose of carboplatin cannot exceed a total dose of 750 mg. Alterations in renal function may require a recalculation of the carboplatin dose.

Cisplatin will be administered at a dose of 100 mg per square meter of BSA as an IV infusion on Cycle Day 1 of a 3-week cycle.

5-FU will be administered at a dose of 1000 mg per square meter of BSA per day as a continuous infusion for 4 days on Cycle Days 1-4 of a 3-week cycle.

Cetuximab will be administered at a dose of 400 mg per square meter of BSA as an IV infusion on Day 1 of the study followed by subsequent weekly doses of 250 mg per square meter as IV infusions.

5.2.1.2 Dose Selection/Modification

The CTCAE version 4.0 (CTCAE 4.0) must be used to grade the severity of AEs. If appropriate, the Investigator may attribute each toxicity event to cisplatin or carboplatin, 5-FU, cetuximab or pembrolizumab alone in the combination arms and use a stepwise dose reduction according to Table 3. If a dose reduction for toxicity occurs with any agent, the dose may not be re-escalated. Dose modifications are always based on the previous cycle.

Subjects can have 2 levels of dose reductions per agent to cisplatin, carboplatin, 5-FU, and cetuximab throughout the course of the study for toxicities as described in Table 3. If further toxicity occurs or the criteria for resuming treatment are not met, the subject must be discontinued from that drug and continue to participate in the study. For pembrolizumab toxicities refer to Table 4, platinum toxicities refer to Table 5 and Table 6, 5-FU toxicities refer to Table 7 and Table 8, and cetuximab toxicities refer to Table 9, Table 10, and Table 11. If a subject experiences several toxicities and there are conflicting recommendations, follow the most conservative dose adjustment recommended (dose reduction appropriate to the most severe toxicity).

Reduction or holding of one agent and not the other agents is appropriate if, in the opinion of the Investigator, the toxicity is clearly related to one of the study drugs. If, in the opinion of the Investigator, the toxicity is related to the combination of 2 agents, both drugs should be reduced or held according to recommended dose modifications. If the toxicity is related to the combination of 3 agents, all 3 agents should be reduced or held according to the recommended dose modifications. If one or more study agent(s) are held for toxicity, the schedule for restarting the agent(s) should correspond with the next treatment cycle once the toxicity has resolved according to the recommended guidelines. Subjects who require more than 2 levels of dose reductions as outlined in Table 3 below to any particular component of the regimen for toxicities will have that agent discontinued.

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

Table 3 Dose Modifications for Trial Medications

	Dose level 0	**Dose level -1**	**Dose level -2**	**Dose level -3**
Cisplatin	100 mg/m^2	80 mg/m^2 (20% decrease)	64 mg/m^2 (20% decrease)	Discontinue
Carboplatin	AUC 5	AUC 4 (20% decrease)	AUC 3 (20% decrease)	Discontinue
5-FU	1000 mg/m^2/day	800 mg/m^2/day (20% decrease)	640 mg/m^2/day (20% decrease)	Discontinue
Cetuximab	400 mg/m^2 then 250 mg/m^2	200 mg/m^2 (20% decrease)	150 mg/m^2 (20% decrease)	Discontinue
Note: Pembrolizumab dose should not be modified for toxicity. See Table 4 for modification of Pembrolizumab dosing schedule for drug-related AEs.				

Investigators may follow the local label for dose modifications. If a toxicity is not otherwise specified, investigators should refer to the label or local standard of care for dose adjustments. Dose modification according to Table 3 is allowable for intolerable Grade 2-3 toxicities not specified in the tables below at the Investigator's discretion. These dose modification decisions must be documented in the subject's study records and in the case report form.

5.2.1.2.1 Dose Modification for Pembrolizumab

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

AEs associated with pembrolizumab exposure may represent an immunologic etiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical trial data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, and skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab and administer corticosteroids. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab are provided in Table 4. See Section 5.6 for supportive care guidelines, including use of corticosteroids.

Table 4 Dose Modification and Toxicity Management Guidelines for Pembrolizumab

General instructions:

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

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

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

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

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

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

5.2.1.2.2 Dose Modifications for Platinum

Investigators may switch subjects from cisplatin to carboplatin during the course of the study if toxicities occur. If the cisplatin dose was modified prior to switching, the subject may start at a carboplatin dose of AUC 5 and will be eligible to receive an additional 2 dose modifications of carboplatin.

Table 5 Dose Modification Guidelines for Febrile Neutropenia or Documented Infection

Adverse Event	Number of Occurrences	Treatment Modification
Febrile neutropenia[a] Documented infection	1	Reduce by 1 DL The use of growth factors and antibiotics should be considered per local standards.
	2	Reduce by 1 DL Consider prophylactic antibiotics for subsequent cycles. The use of growth factors should be strongly considered per local standards.
	3	Discontinue platinum
a. ANC <1000/mm3 (1.0 x 10^9/L) and a single temperature >38.3C or sustained temperature ≥38C for >1 hour.		

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

Category	Toxicity	Hold Platinum Treatment for Grade	Timing for Restarting Platinum Treatment	Dose for Restarting Platinum Treatment	Discontinue Platinum
Hematologic	Neutropenia	3[1]	Neutrophil count resolves to ≥1,000/mm^3 (1.0 x 10^9/L)	No Reduction *consider G-CSF	Toxicity does not resolve within 12 weeks of last infusion or if >2 Dose Level reductions exceeded
		4[1]	Neutrophil count resolves to ≥1,000/mm^3 (1.0 x 10^9/L)	Reduce by 1 DL *consider G-CSF	Toxicity does not resolve within 12 weeks of last infusion or if >2 Dose Level reductions exceeded
	Thrombocytopenia	2	Platelet count resolves to ≥75,000/mm^3 (75 x 10^9/L) or baseline	No reduction	Toxicity does not resolve within 12 weeks of last infusion or if >2 Dose Level reductions exceeded
		3-4[1]	Platelet count resolves to ≥75,000/mm^3 (75 x 10^9/L)or baseline	Reduce by 1 DL	Toxicity does not resolve within 12 weeks of last infusion or if >2 Dose Level reductions exceeded

Category	Toxicity	Hold Platinum Treatment for Grade	Timing for Restarting Platinum Treatment	Dose for Restarting Platinum Treatment	Discontinue Platinum
Non-hematologic	Creatinine Increased	2-4[1]	Toxicity resolves to Grade 0-1	For subjects taking Carboplatin, reduce by 1 DL For subjects taking Cisplatin, change Cisplatin to Carboplatin	Toxicity does not resolve within 12 weeks of last infusion or if >2 Dose Level reductions exceeded
	Ototoxicity or Sensory neuropathy	2	Change Cisplatin to Carboplatin May continue treatment with Carboplatin		
		3-4	May switch Cisplatin to Carboplatin if resolved to Grade ≤2 within 12 weeks of last infusion If already using carboplatin, then discontinue		
	All other non-hematologic toxicities[2]	3-4[1]	Toxicity resolves to Grade 0-1	Reduce by 1 DL	Toxicity does not resolve within 12 weeks of last infusion or if >2 Dose Level reductions exceeded
	Laboratory adverse event[2]	4	Toxicity resolves to Grade 2 or less	Reduce by 1 DL	Toxicity does not resolve within 12 weeks of last infusion or if >2 Dose Level reductions exceeded

[1]*Permanent discontinuation should be considered for any severe or life-threatening event. Consult Sponsor before restarting treatment after Grade 4 drug-related AE*
[2]Patients with intolerable or persistent Grade 2 drug-related AE may hold at physician discretion. Permanently discontinue from agent for persistent Grade 2 adverse reactions for which treatment has been held, and did not recover to Grade 0-1 within 12 weeks of the last dose. 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.

5.2.1.2.3 Dose Modifications for 5-Fluorouracil

Table 7 Dose Modification Guidelines for Febrile Neutropenia or Documented Infection

Adverse Event	Number of Occurrences	Treatment Modification
Febrile neutropenia[a] Documented infection	1	Reduce by 1 DL The use of growth factors and antibiotics should be considered per local standards.
	2	Reduce by 1 DL. Consider prophylactic antibiotics for subsequent cycles. The use of growth factors should be strongly considered per local standards.
	3	Discontinue 5-FU

a. ANC <1000/mm3 and a single temperature >38.3C or sustained temperature ≥38C for >1 hour.

Table 8 Dose Modification Guidelines for 5-Fluorouracil Drug-Related Adverse Events

Category	Toxicity	Hold 5-FU Treatment for Grade	Timing for Restarting 5-FU Treatment	Dose for Restarting 5-FU Treatment	Discontinue 5-FU
Hematologic	Neutropenia	3[1]	Neutrophil count resolves to ≥1,000/mm^3 (1.0 x 10^9/L)	No Reduction *consider G-CSF	Toxicity does not resolve within 12 weeks of last infusion or if >2 Dose Level reductions exceeded
		4[1]	Neutrophil count resolves to ≥1,000/mm^3 (1.0 x 10^9/L)	Reduce by 1 DL *consider G-CSF	Toxicity does not resolve within 12 weeks of last infusion or if >2 Dose Level reductions exceeded
	Thrombocytopenia	2	Platelet count resolves to ≥75,000/mm^3 (75 x 10^9/L) or baseline	No reduction	Toxicity does not resolve within 12 weeks of last infusion or if >2 Dose Level reductions exceeded
		3-4[1]	Platelet count resolves to ≥75,000/mm^3 (75 x 10^9/L) or baseline	Reduce by 1 DL	Toxicity does not resolve within 12 weeks of last infusion or if >2 Dose Level reductions exceeded
Non-hematologic	Creatinine Increased	2-4[1]	Toxicity resolves to Grade 0-1	No reduction	Toxicity does not resolve within 12 weeks of last infusion or if >2 Dose Level reductions exceeded
	Mucositis Diarrhea	2-4[1]	Toxicity resolves to Grade 0-1	Reduce by 1 DL	Toxicity does not resolve within 12 weeks of last infusion or if >2 Dose Level reductions exceeded
	Hand-foot syndrome	2	Toxicity resolves to Grade 0-1	No reduction	Toxicity does not resolve within 12 weeks of last infusion or if >2 Dose Level reductions exceeded
		3-4[1]	Toxicity resolves to Grade 0-1	Reduce by 1 DL	Toxicity does not resolve within 12 weeks of last infusion or if >2 Dose Level reductions exceeded
	All other non-hematologic toxicities[2]	3-4[1]	Toxicity resolves to Grade 0-1	Reduce by 1 DL	Toxicity does not resolve within 12 weeks of last infusion or if >2 Dose Level reductions exceeded
	Laboratory adverse event[2]	4	Toxicity resolves to Grade 2 or less	Reduce by 1 DL	Toxicity does not resolve within 12 weeks of last infusion or if >2 Dose Level reductions exceeded

[1]*Permanent discontinuation should be considered for any severe or life-threatening event. Consult Sponsor before restarting treatment after Grade 4 drug-related AE*
[2]Patients with intolerable or persistent Grade 2 drug-related AE may hold at physician discretion. Permanently discontinue from agent for persistent Grade 2 adverse reactions for which treatment has been held, and did not recover to Grade 0-1 within 12 weeks of the last dose. 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.

5.2.1.2.4 Dose Modifications for Cetuximab

For any delayed cetuximab treatment, do not repeat the initial dose of 400 mg/m². At the restart of cetuximab treatment, all subsequent infusions will be at the appropriate dose level according to Table 9, Table 10, and Table 11. If a subject develops a toxicity that mandates interruption of therapy, the toxicity must resolve within 12 weeks from the last dose of cetuximab or the drug should be discontinued with the exception of a subject who is clinically benefiting from cetuximab treatment. In this case, the investigator may request the Sponsor to allow the subject to continue to receive cetuximab.

Cetuximab therapy will not be delayed for chemotherapy-related toxicity. If chemotherapy administration is delayed, the subject may continue to receive weekly infusions of cetuximab. After resolution of toxicity, platinum and/or 5-FU may be restarted at any weekly visit when cetuximab is given (i.e. Day 8 or Day 15 of a cycle). The interval between platinum and/or 5-FU infusions will continue as every 3 weeks from the time of the restart. If subjects on the cetuximab + platinum + 5-FU arm are required to have the platinum and/or 5-FU discontinued for toxicity, the subject and may continue to receive cetuximab alone. In the case of cetuximab toxicity, subjects may continue on chemotherapy alone.

Table 9 Dose Modification Guidelines for Cetuximab Drug-Related Adverse Events

Category	Toxicity	Hold Cetuximab Treatment for Grade	Timing for Restarting Cetuximab Treatment	Dose for Restarting Cetuximab Treatment	Discontinue Cetuximab
Non-Hematologic	Infusion Reaction	2-4	See section 5.2.1.2.4 and Table 10		
	Rash	3-4	See section 5.2.1.2.4 and Table 11		
	All other non-hematologic toxicities[1]	3-4	Toxicity resolves to Grade 0-1	Reduce by 1 DL	Toxicity does not resolve within 12 weeks of last infusion or if >-2 Dose Level reductions exceeded
	Laboratory Adverse Events[2]	4	Toxicity resolves to Grade 2 or less	Reduce by 1 DL	Toxicity does not resolve within 12 weeks of last infusion or if >-2 Dose Level reductions exceeded

Note: Permanent discontinuation should be considered for any severe or life-threatening event. Consult Sponsor before restarting treatment after Grade 4 drug related AE.
[1] Patients with intolerable or persistent Grade 2 drug-related AE may hold at physician discretion. Permanently discontinue from agent for persistent Grade 2 adverse reactions for which treatment has been held, and did not recover to Grade 0-1 within 12 weeks of the last dose.
[2] 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.

Infusion Reactions

Subjects who experience cetuximab-related infusion reactions should have cetuximab reduced according to Table 10 and continue to receive antihistamine premedication prior to administration. Once the cetuximab infusion rate has been decreased due to an allergic/hypersensitivity reaction, it should remain decreased for all subsequent infusions.

If the subject experiences a second infusion reaction at the decreased rate, cetuximab must be discontinued. If any Grade 3-4 infusion reaction occurs, cetuximab treatment must be

discontinued immediately. Subjects who experience serious infusion reactions will be discontinued from cetuximab. The subject may continue to receive chemotherapy as scheduled.

Table 10 Cetuximab Dose Modification for Infusion Reactions

CTCAE Grade	Hold Treatment (Y/N)	Dose for Restarting Treatment
1	N	Decrease the cetuximab infusion rate by 50% and monitor closely for any worsening. **Note:** The total infusion time for cetuximab should not exceed 4 hours.
2	Y Stop cetuximab infusion and administer bronchodilators, oxygen, etc. as medically indicated.	Resume infusion at 50% of previous rate once allergic/hypersensitivity reaction has resolved or decreased to Grade 1 in severity, and monitor closely for any worsening
3-4	Y Stop the cetuximab infusion immediately and disconnect infusion tubing from the subject	Stop the cetuximab infusion immediately and disconnect infusion tubing from the subject. Administer epinephrine, bronchodilators, antihistamines, glucocorticoids, intravenous fluids, vasopressor agents, oxygen, etc., as medically indicated. **Subjects must discontinue treatment with cetuximab permanently.**

Dermatologic Toxicity

The dosing of cetuximab will be omitted 1 to 2 weeks in the case of severe (Grade 3 or 4) acneiform rash. If acneiform rash improves during this time, then the dose of cetuximab should be reduced as indicated in Table 11. The dose modification guidelines in Table 9 should be followed for dermatologic toxicities other than acneiform rash.

If acneiform rash does not improve during this time, cetuximab will be discontinued.

Subjects who have held cetuximab therapy for more than 2 consecutive infusions due to acneiform rash, and upon resolution of the toxicity are still felt to be benefiting from cetuximab treatment may resume cetuximab with Sponsor approval.

Table 11 Cetuximab Dose Modification for Severe Acneiform Rash

Severe Acneiform Rash (≥ Grade 3)	Dose Interruption	Outcome	Dose Modification
1st occurrence	Omit 1-2 doses	Improved[a]	None, continue at same dose
2nd occurrence	Omit 1-2 weeks	Improved[a]	Permanently reduce by 1 dose level [b]
3rd occurrence	Omit 1-2 weeks	Improved[a]	Permanently reduce by another dose level [b]
4th occurrence	Discontinue	N/A	N/A

a. If rash does not improve, then discontinue cetuximab.
b. Discontinue cetuximab if dose is less than 150 mg/m^2

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 5 days after randomization is permitted).

Trial treatment of cisplatin, carboplatin, 5-FU, 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 5 days after randomization is permitted). The ±3 day window for cetuximab generally applies to restarting cetuximab after a treatment delay; administering cetuximab with less than 7 days between doses is not recommended.

Subjects may receive a maximum of 6 cycles (infusions) of the chemotherapy agents (carboplatin, cisplatin, and 5-FU).

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

5.2.2.1 Pembrolizumab

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

Pembrolizumab will be administered as a dose of 200 mg using a 30-minute IV infusion. 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 between -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 and administration of infusion solution.

For subjects randomized to the pembrolizumab plus chemotherapy arm, the pembrolizumab infusion is administered first followed by the platinum and 5-FU infusions.

5.2.2.2 Carboplatin

Carboplatin will be administered on Day 1 of each treatment cycle after completion of all procedures and assessments are completed according to the Trial Flow Chart in Section 6.0.

Carboplatin is given as a dose of AUC 5 using infusion duration of 60 minutes (or infusion duration according to local practice).

5.2.2.3 Cisplatin

Cisplatin will be administered on Day 1 of each treatment cycle after completion of all procedures and assessments are completed according to the Trial Flow Chart in Section 6.0.

Cisplatin is given as a dose of 100 mg/m^2 using infusion duration of 60 minutes (or infusion duration according to local practice).

5.2.2.4 5-Fluorouracil

5-FU will be administered as a dose of 1000 mg/m^2/day as a continuous infusion from Day 1 to Day 4 of each treatment cycle.

On Day 1 of each treatment cycle, the 5-FU infusion should be started after completion of all procedures and assessments according to the Trial Flow Chart in Section 6.0.

5.2.2.5 Cetuximab

Trial treatment with 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/m^2 with infusion time of 120 minutes (maximum infusion rate 10 mg/min). For subsequent infusions, the cetuximab dose is 250 mg/m^2 with infusion duration of 60 minutes (maximum infusion rate 10 mg/min) for all doses starting with the Cycle 1 Day 8 administration.

For subjects in the Standard Treatment Arm (cetuximab plus chemotherapy), the cetuximab infusion is administered followed by the platinum and 5-FU infusions. After platinum and 5-FU are discontinued, for subjects with at least stable disease, cetuximab monotherapy may continue until disease progression or unacceptable toxicity occurs.

5.2.3 Trial Blinding/Masking

This is an open-label trial; therefore the Sponsor, investigator and subject will know the treatment administered to an individual subject. Imaging data for the primary analysis will be centrally reviewed by independent radiologist(s) without knowledge of subject treatment assignment or PD-L1 biomarker results.

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 manager, unblinded Sponsor statistician, and unblinded Sponsor statistical programmer who will be responsible for data review to ensure validity of results but 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 3 treatment arms. Subjects will be assigned randomly in a 1:1:1 ratio to the treatment arms as follows:

1. Pembrolizumab Monotherapy Arm:

   Pembrolizumab (200 mg Q3W)

2. Pembrolizumab plus Chemotherapy Arm:

   Pembrolizumab (200 mg Q3W) + [Cisplatin (100 mg/m^2 Q3W) or Carboplatin (AUC 5 Q3W)] + 5-FU (1000 mg/m^2/day 4-day infusion Q3W)

3. Cetuximab plus Chemotherapy Arm:

   Cetuximab 400 mg/m^2 then 250 mg/m^2 QW + [Cisplatin (100 mg/m^2 Q3W) or Carboplatin (AUC 5 Q3W)] + 5-FU (1000 mg/m^2/day 4-day infusion Q3W)

5.4 Stratification

Randomization will be stratified according to the following factors:

1. PD-L1 tumor expression as determined by PD-L1 immunohistochemistry (strongly positive vs. not strongly positive)

   Note: *Strongly positive* includes those subjects whose tumor expression levels are ≥50%. *Not strongly positive* includes those subjects whose tumor expression levels are <50%, or are not able to be determined for any reason.

2. HPV status for oropharynx cancer as determined by p16 immunohistochemistry (IHC) (positive vs. negative); HPV status for subjects without oropharynx cancer (e.g. cancers of the oral cavity, hypopharynx and larynx) is considered HPV negative.

3. Eastern Cooperative Oncology Group (ECOG) Performance Scale (0 vs. 1)

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 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.

Prescription pain medications should be entered into the CRF using the information recorded by the subject on the Pain Medication Log. For prescription pain medications recorded on the Pain Medication Log, changes in drug dosage, total daily dose, route, and dates should be documented on the CRF.

All concomitant medications received from first dose of trial treatment through 30 days after the last dose of trial treatment should be recorded in the CRF. Medications administered more than 30 days after the last dose of trial treatment should be recorded for SAEs and ECIs as defined in Section 7.2.

5.5.2 Prohibited Concomitant Medications

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

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab
- Radiation therapy
    - Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be considered 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 the cetuximab + platinum + 5-FU therapy to receive live vaccines while participating in the trial.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an AE. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor. Additionally, a short, limited course of steroids may be used to treat medical conditions and/or AEs during the study after Sponsor notification and consultation.
    - Note: For subjects randomized to the standard treatment arm (cetuximab plus chemotherapy) the use of systemic glucocorticoids on trial treatment is acceptable and may be required for premedication.
    - Note: Inhaled steroids are allowed for management of asthma/ COPD.
    - Note: Use of prophylactic corticosteroids to avoid allergic reactions (e.g., to IV contract dye) or use of corticosteroids as pre-medication for chemotherapeutic agents specified in the protocol is permitted.

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

The Exclusion Criteria describe 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 AEs with potential immunologic etiology are outlined. 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: 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.

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

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

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

  Thyroid disorders can occur at any time during treatment. Monitor patients for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders.
    - **Grade 2** hyperthyroidism events (and **Grade 2-4** hypothyroidism):
        - In hyperthyroidism, non-selective beta-blockers (e.g. propranolol) are suggested as initial therapy.
        - In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or 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 improve to Grade 1 or less, a steroid taper should be started and continued over no less than 4 weeks.
- **Renal Failure or Nephritis**:
    - For **Grade 2** events, treat with corticosteroids.
    - For **Grade 3-4** events, treat with systemic corticosteroids.
    - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

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

  Table 12 below shows treatment guidelines for subjects who experience an infusion reaction associated with administration of pembrolizumab (MK-3475).

Table 12 Infusion Reaction Treatment Guidelines

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

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 4: Life-threatening; pressor or ventilatory support indicated	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.**	
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 Cisplatin and Carboplatin

The following guidelines may be used for subjects in the pembrolizumab plus chemotherapy arm.

Prevention and/or treatment of nausea and vomiting should be managed with:

1. Emend (aprepitant) 150 mg IV or Emend 3 day pack 125 mg day 1, 80 mg day 2, 80 mg day 3
2. Plus Aloxi (palonosetron) 0.25 mg IV

Additionally, nausea may be managed with:

1. Zofran (ondansetron) 8 mg twice a day; or
2. Compazine (prochlorperazine) 10 mg 3-4 times per day

For subjects randomized to the standard treatment arm (cetuximab plus chemotherapy) the use of systemic glucocorticoids during trial treatment is acceptable and may be required for premedication.

Initial use of dexamethasone is limited to no more than 8 mg administered on Day 1 of a treatment cycle before study treatment. Need for additional dexamethasone must be discussed with the Sponsor. Dexamethasone should be administered prior to study treatment.

Please refer to the product label or local standards of care for additional cisplatin and carboplatin supportive measures.

5.6.3 Supportive Care Guidelines for 5-FU

Please refer to the product label or local standards of care for 5-FU supportive measures.

5.6.4 Supportive Care Guidelines for Cetuximab

Subjects receiving cetuximab should be pre-medicated 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 12 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

Pembrolizumab, carboplatin, cisplatin, 5-FU and cetuximab may have adverse effects on a fetus in utero. Furthermore, it is not known if carboplatin, cisplatin, 5-FU and cetuximab 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 2 birth control methods can be either 2 barrier methods or a barrier method plus a hormonal method to prevent pregnancy. Subjects should start using birth control from study Visit 1 throughout the study period up to 180 days after the last dose of study therapy.

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

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 (e.g., Sweden and Norway) or sites that follow the Clinical Trial Facilitation Group (CTFG) guidance, please use the following:

Pembrolizumab, carboplatin, cisplatin, 5-FU and cetuximab may have adverse effects on a fetus in utero. Furthermore, it is not known if carboplatin, cisplatin, 5-FU and cetuximab 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 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 should start using birth control from study Visit 1 throughout the study period up to 180 days after the last dose of study therapy.

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 on any arm of this study, the subject will immediately be discontinued from study treatment. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been

completed or terminated. The outcome of the pregnancy will be reported to the Sponsor without delay and within 24 hours if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor. If a male subject impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to the Sponsor and followed as described above and in Section 7.2.2.

5.7.4 Use in Nursing Women

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

5.7.4.1 Pembrolizumab

It is unknown whether pembrolizumab is excreted in human milk.

5.7.4.2 Cetuximab

It is not known whether cetuximab is secreted in human milk. IgG antibodies, such as cetuximab, can be excreted in human milk.

5.7.4.3 Cisplatin

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

5.7.4.4 Carboplatin

It is not known whether carboplatin is excreted in human milk. Because there is a possibility of toxicity in nursing infants secondary to carboplatin treatment of the mother, it is recommended that breast feeding be discontinued if the mother is treated with carboplatin injection.

5.7.4.5 5-FU

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

5.8 Subject Withdrawal/Discontinuation Criteria

5.8.1 Discontinuation of Treatment

Discontinuation of treatment does not represent withdrawal from the trial.

As certain data on clinical events beyond treatment discontinuation may be important to the study, they must be collected through the subject's last scheduled follow-up, even if the subject has discontinued treatment. Therefore, all subjects who discontinue trial treatment prior to completion of the treatment will still continue to participate in the trial as specified in Section 6.0 - Trial Flow Chart and Section 7.1.5.3 – Post-Treatment Visits.

Subjects may discontinue treatment at any time for any reason or be dropped from treatment at the discretion of the investigator should any untoward effect occur. In addition, a subject may be discontinued from treatment by the investigator or the Sponsor if treatment is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding procedures to be performed at treatment discontinuation are provided in Section 7.1.4 – Other Procedures.

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

- The subject or subject's legally acceptable representative requests to discontinue treatment.
- Radiographic disease progression <u>as determined by central imaging vendor</u>

  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 withdraw the subject
- The subject has a confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements
- The subject is lost to follow-up
- Completed 24 months of treatment with pembrolizumab

  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 AE monitoring (serious adverse events will be collected for 90 days after the end of treatment as described in Section 7.2.3.1). Subjects who discontinue for reasons other than PD will have post-treatment follow-up for disease status until centrally-

verified 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 survival until death, withdrawal of consent, or the end of the study, whichever occurs first.

5.8.1.1 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.

Pembrolizumab Monotherapy and Pembrolizumab Plus Chemotherapy Arms

If radiologic imaging by the central imaging vendor shows 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. 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 PD, 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.

The decision to continue study treatment after the first evidence of disease progression determined by the central imaging vendor is at the Investigator's discretion based on the clinical status of the subject as described in Table 13 in Section 7.1.2.6.3.1.

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 PS
- Absence of rapid progression of disease
- Absence of progressive tumor at critical anatomical sites (e.g., cord compression) requiring urgent alternative medical intervention

Standard Treatment Arm

Confirmation of progression does not apply to subjects randomized to the standard treatment arm. Subjects on the standard treatment arm should discontinue treatment with study medication after radiologic PD is verified by the central imaging vendor.

5.8.1.2 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 2 treatments with pembrolizumab beyond the date when the initial CR was declared. Subjects who then experience centrally-verified radiographic disease progression may be eligible for up to 1 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
- The trial is ongoing.

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.

For subjects who are discontinued from treatment but continue to be monitored in the trial, see Section 6.0 – Trial Flow Chart, and Section 7.1.5.3 – Post-Treatment Visits for those procedures to be completed at each specified visit.

Subjects may be allowed to begin treatment again if deemed medically appropriate, and provided the subject meets the criteria specified in Section 7.1.5.2.1 – Second Course Phase (Retreatment Period).

5.8.2 Withdrawal from the Trial

Subjects may withdraw from the trial at any time for any reason. If a subject withdraws from the trial, they will no longer receive treatment or be followed at scheduled protocol visits.

A subject must be withdrawn from the trial if:

- The subject or subject's legally acceptable representative withdraws consent from the trial.
- The subject is lost to follow-up.

Specific details regarding procedures to be performed at the time of withdrawal from the trial including specific details regarding withdrawal from Future Biomedical Research are outlined in Section 7.1.4 – Other Procedures.

5.9 Subject Replacement Strategy

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

5.10 Beginning and End of the Trial

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

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 safety at the recommendation of the Data Monitoring Committee (DMC). Section 7.3.3 describes the DMC and its responsibilities.

6.0 TRIAL FLOW CHART

6.1 Initial Treatment Phase

6.1.1 Pembrolizumab and Pembrolizumab plus Chemotherapy Arms

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	Discontinuation	Safety Follow-up	Follow Up Visits[b]	Survival Follow-up[c]
Scheduling Window (Days)[d]:	-28 to -1	+5[d]	± 3	± 3	± 3	± 3	± 3	At time of treatment discon	30 days after last dose of study medication (± 3 days)	Every 6 weeks post discon or per footnote	Every 12 weeks (± 14 days)
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				
Prior Treatment for Head and Neck Cancer	X										
Post-study Anticancer Therapy Status										X	X
Survival Status[c]		< ----------									> X
Clinical Procedures/Assessments											
Disease Details	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	Discontinuation	Safety Follow-up	Follow Up Visits[b]	Survival Follow-up[c]
Scheduling Window (Days)[d]:	-28 to -1	+5[d]	± 3	± 3	± 3	± 3	± 3	At time of treatment discon	30 days after last dose of study medication (± 3 days)	Every 6 weeks post discon or per footnote	Every 12 weeks (± 14 days)
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, Weight, and Height[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]										
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 (total or free), FT4 and TSH[o]	X[n]		X		X		X[j]		X[p]		
Laboratory Procedures/Assessments: analysis performed by CENTRAL laboratory											
Pharmacokinetics[q]		X[q]	X[q]		X[q]						
Anti-pembrolizumab Antibodies[q]		X[q]	X[q]		X[q]						

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	Discontinuation	Safety Follow-up	Follow Up Visits[b]	Survival Follow-up[c]
Scheduling Window (Days)[d]:	-28 to -1	+5[d]	± 3	± 3	± 3	± 3	± 3	At time of treatment discon	30 days after last dose of study medication (± 3 days)	Every 6 weeks post discon or per footnote	Every 12 weeks (± 14 days)
Blood for Genetics[r,y]		X									
Correlative Blood Samples for DNA[s]		X	X	X				X			
Correlative Blood Samples for RNA[s]		X	X	X				X			
Correlative Blood Samples for plasma[s]		X									
Correlative Blood Samples for serum[s]		X									
Efficacy Measurements											
Tumor Imaging and RECIST Assessment	X[t]				X[u]		X[u]	X[b,v]		X[b]	
Tumor Tissue Collection											
Archival or Newly Obtained Tissue Collection for Subjects with Oropharynx Cancer Tested Locally for HPV Status for Stratification (newly obtained may be obtained 90 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 90 days prior to treatment initiation). Tissue sample for FBR.	X[w]										
Patient Reported Outcomes											
EuroQol EQ-5D[x]		X	X	X	X[j]		X[j]	X	X[x]		
EORTC QLQ-C30[x]		X	X	X	X[j]		X[j]	X	X[x]		

Trial Period:	Screening Phase	Treatment Cycles (3-Week Cycles)[a]						End of Treatment	Post-Treatment		
						To be repeated beyond 6 cycles					
Treatment Cycle/Title:	Screening (Visit 1)	1	2	3	4	5	6	Discontinuation	Safety Follow-up	Follow Up Visits[b]	Survival Follow-up[c]
Scheduling Window (Days)[d]:	-28 to -1	+5[d]	± 3	± 3	± 3	± 3	± 3	At time of treatment discon	30 days after last dose of study medication (± 3 days)	Every 6 weeks post discon or per footnote	Every 12 weeks (± 14 days)
EORTC QLQ-H&N 35[x]		X	X	X	X[j]		X[j]	X	X[x]		
Pain Medication Log[x]	X	X	X	X	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. For subjects in the pembrolizumab plus chemotherapy arm, subjects may receive a maximum of 6 cycles (infusions) of platinum and 5-FU. Pembrolizumab treatment may continue after discontinuation of chemotherapy. Imaging should be performed at 9 weeks after randomization 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) (or every 9 weeks ±7 days after the first year) until (1) the start of new anti-cancer treatment, (2) disease progression as assessed by the central imaging vendor, (3) death, or (4) the end of the study, whichever occurs first. The first follow-up imaging assessment should occur 6 weeks (±7 days) from the last scheduled on-treatment imaging timepoint (or 9 weeks ±7 days from the last scheduled on–treatment imaging timepoint after the first year).
c. After the start of new anti-cancer treatment or documented disease progression by the central imaging vendor, whichever occurs first, the subject enters the Survival Follow Up Phase and should be contacted by telephone approximately every 12 weeks to assess for survival status. Updated survival status may be requested by the Sponsor at any time during the course of the study. Upon Sponsor notification, all subjects who do not/will not have a scheduled study visit or study contact during the Sponsor defined time period will be contacted for their survival status (excluding subjects that have a death event previously recorded).
d. In general, the window for each visit is ±3 days unless otherwise noted. Cycle 1 treatment should be given within 5 days of randomization.
e. Written 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 before the first dose of trial treatment. Concomitant medications – Enter new medications started from the first dose of trial treatment through 30 days after the last dose of trial treatment. 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 following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever comes first. Afterwards, report only SAEs and ECIs that are related to trial treatment.
j. To be repeated every 2 cycles after Cycle 4. ePROs will continue up to 1 year.
k. Vital signs to include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at visit 1 only.

l.	For women of reproductive potential, a serum pregnancy test should be performed within 72 hours prior to first dose of trial treatment. A urine test can be considered if serum is not appropriate. Pregnancy tests (serum and/or urine tests) should be repeated if required by local guidelines.
m.	Coagulation factors (PT/INR and aPTT) should be tested as part of the screening procedures for all subjects. PTT may be performed if the local lab is unable to perform aPTT. 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. Screening labs must be collected and assessed prior to randomizing the subject. ECOG must be 0 or 1 on the first day of dosing. 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.	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.	For subjects in the pembrolizumab and pembrolizumab plus chemotherapy arms, pre-dose trough PK and anti-pembrolizumab antibody samples will be collected at Cycles 1, 2, 4, 8 and every 4 cycles thereafter. All pre-dose trough samples should be drawn within 24 hours before infusion of pembrolizumab. Additional post-dose peak PK samples will be drawn within 30 minutes after end of pembrolizumab infusion at Cycles 1 and 8.
r.	This sample should be drawn for planned 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. Detailed instructions for the collection and management of specimens are provided in the Procedures Manual.
s.	See Section 7.1.2.7 and the Study Procedures Manual for correlative blood sample information. Detailed instructions are provided in the Procedures Manual.
t.	The initial tumor imaging will be performed within 28 days prior to randomization. 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. 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.
u.	The first on-study imaging time point will be performed at 9 weeks (±7 days) after the date of randomization and then every 6 weeks (±7 days) thereafter or more frequently if clinically indicated. After 1 year, imaging time point will occur every 9 weeks (±7 days). Imaging timing should follow calendar days and should not be adjusted for delays in cycle starts or extension of pembrolizumab cycle frequencies. The same imaging technique should be used in a subject throughout the trial. On-study scans should be submitted immediately to the central imaging vendor and progressive disease should be verified by the central imaging vendor prior to subject discontinuation from treatment. 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.
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 is not 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 for HPV status (if HPV status not known) prior to randomization for stratification. Baseline tumor tissue must also be provided to the central vendor for PD-L1 biomarker testing prior to randomization for stratification. Refer to Section 7.1.2.7 for additional information about tissue requirements. 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 a best practice and strongly recommended that ePROs are administered to randomized subjects prior to drug administration, adverse event evaluation, and disease status notification. All ePROs are to be performed prior to dosing at Cycle 1, Cycle 2, Cycle 3, Cycle 4 and every 2 cycles thereafter (e.g., Cycle 6, Cycle 8, Cycle 10) up to 1 year from treatment initiation or End of Treatment, whichever occurs first, and at the 30-day Safety Follow-up Visit. If the subject does not complete the ePROs for any reason, the Miss Mode form must be completed to capture the reason the assessment was not performed. The Pain Medication Log should be collected at all scheduled visits from Screening through the Safety Follow-up Visit (see Section 4.2.3.6.4).
y.	This sample should be drawn for planned, exploratory genetic analysis of DNA unless there is either a documented law or regulation prohibiting collection, or unless the IRB/IEC does not approve of the collection.

6.1.2 Standard Treatment Arm (Cetuximab plus Chemotherapy)

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]
Treatment Day		1	8	15	1	8	15	1	8	15	1	8	15	1	8	15	1	8	15				
Scheduling Window (Days)[d]:	-28 to -1	+5[d]	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of treatmentdiscon	30 days after last dose of study medication (± 3 days)	Every 6 weeks post discon or per footnote	Every 12 weeks (± 14 days)
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[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Prior treatment for head and neck cancer	X																						
Trial Treatment Administration		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
Clinical Procedures/Assessments																							
Disease details	X																						
Review Adverse Events[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																						

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]
Treatment Day		1	8	15	1	8	15	1	8	15	1	8	15	1	8	15	1	8	15				
Scheduling Window (Days)[d]:	-28 to -1	+5[d]	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of treatmentdiscon	30 days after last dose of study medication (± 3 days)	Every 6 weeks post discon or per footnote	Every 12 weeks (± 14 days)
Full Physical Examination	X																			X			
Directed Physical Examination		X			X			X			X			X			X						
Vital Signs, Weight, and Height[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																						
CBC with Differential[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[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 (total or free), FT4 and TSH[o]	X[n]				X						X						X[j]				X[p]		
Laboratory Procedures/Assessments: analysis performed by CENTRAL laboratory																							
Blood for Genetics[w]		X																					
Correlative Blood Samples for DNA[q]		X			X			X												X			
Correlative Blood Samples for RNA[q]		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			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]:	-28 to -1	+5[d]	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of treatmentdiscon	30 days after last dose of study medication (± 3 days)	Every 6 weeks post discon or per footnote	Every 12 weeks (± 14 days)
Correlative Blood Samples for plasma[q]		X																					
Correlative Blood Samples for serum[q]		X																					
Efficacy Measurements																							
Tumor Imaging and RECIST assessment	X[r]										X[s]						X[s]			X[b,t]		X[b]	
Tumor Tissue Collection																							
Archival or Newly Obtained Tissue Collection for Subjects with Oropharynx Cancer Tested Locally for HPV Status for Stratification (newly obtained may be obtained 90 days prior to treatment initiation)[u]	X[u]																						
Newly Obtained Tissue Collection for Biomarker Analysis (tested centrally) On all Subjects Prior to Randomization for Stratification (may be obtained 90 days prior to treatment initiation)[u]. Tissue sample for FBR.	X[u]																						

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]
Treatment Day		1	8	15	1	8	15	1	8	15	1	8	15	1	8	15	1	8	15				
Scheduling Window (Days)[d]:	-28 to -1	+5[d]	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of treatmentdiscon	30 days after last dose of study medication (± 3 days)	Every 6 weeks post discon or per footnote	Every 12 weeks (± 14 days)
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]		
Pain Medication Log[v]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		

a. In general, assessments/procedures are to be performed prior to the treatment dose. Carboplatin and cisplatin will be dosed on Day 1 of each 3-week cycle. 5-FU will be dosed continuously on Days 1-4 of each 3-week cycle. Subjects may receive a maximum of 6 cycles of platinum and 5-FU. Cetuximab will be dosed on Days 1, 8 and 15 of each 3-week cycle. After discontinuing chemotherapy, cetuximab treatment may continue until disease progression or unacceptable toxicity occurs. Imaging should be performed at 9 weeks after randomization 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) (or every 9 weeks ±7 days after the first year) until (1) the start of new anti-cancer treatment, (2) disease progression as assessed by the central imaging vendor, (3) death, or (4) the end of the study, whichever occurs first. The first follow-up imaging assessment should occur 6 weeks (±7 days) from the last scheduled on-treatment imaging timepoint (or 9 weeks ±7 days from the last scheduled on–treatment imaging timepoint after the first year).

c. After the start of new anti-cancer treatment or documented disease progression by the central imaging vendor, whichever occurs first, the subject enters the Survival Follow Up Phase and should be contacted by telephone approximately every 12 weeks to assess for survival status. Updated survival status may be requested by the Sponsor at any time during the course of the study. Upon Sponsor notification, all subjects who do not/will not have a scheduled study visit or study contact during the Sponsor defined time period will be contacted for their survival status (excluding subjects that have a death event previously recorded).

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

e. Written 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 before the first dose of trial treatment. Concomitant medications – Enter new started from the first dose of trial treatment through 30 days after the last dose of trial treatment. 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

following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever comes first. Afterwards, report only SAEs and ECIs that are related to trial treatment.

j. To be repeated every 2 cycles after Cycle 4. 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. PTT may be performed if the local lab is unable to perform aPTT. 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. Screening labs must be collected and assessed prior to randomizing the subject. ECOG must be 0 or 1 on the first day of dosing. See Section 7.1.3 for details regarding laboratory tests.

o. After screening, labs should be taken on day of treatment or labs may be drawn up to 72 hours prior to dosing if acceptable per local standard of care. See Section 7.1.3 for details regarding laboratory tests. T3 or FT3 can be assayed based on local standards.

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. See Section 7.1.2.7 correlative blood sample information. 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. 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. 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.

s. The first on-study imaging time point will be performed at 9 weeks (±7 days) after the date of randomization, 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 progression should be submitted immediately to the central imaging vendor and progressive disease should be verified by the central imaging vendor prior to subject discontinuation from treatment. 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.

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 is not 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 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. Refer to Section 7.1.2.7 for additional information about tissue requirements. 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 a best practice and strongly recommended that ePROs are administered to randomized subjects prior to drug administration, adverse event evaluation, and disease status notification. All ePROs are to be performed prior to dosing at Cycle 1, Cycle 2, Cycle 3, Cycle 4 and every 2 cycles thereafter (e.g., Cycle 6, Cycle 8, Cycle 10) up to 1 year from treatment initiation or End of Treatment, whichever occurs first, and at the 30-day Safety Follow-up Visit. If the subject does not complete the ePROs for any reason, the Miss Mode form must be completed to capture the reason the assessment was not performed. The Pain Medication Log should be collected at all scheduled visits from Screening through the Safety Follow-up Visit (see Section 4.2.3.6.4).

w. This sample should be drawn for planned 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. Detailed instructions for the collection and management of specimens are provided in the Procedures Manual.

6.2 Second Course Phase – Retreatment with Pembrolizumab

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 Second Course treatment discon	30 days after last dose of study medication (± 3 days)	Every 6 weeks post discon or per footnote	Every 12 weeks (± 14 days)
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[r]		
Chemistry Panel[o]	X[n]	X	X	X	X	X	X	X[r]		
T3, FT4 and TSH[o]	X[n]		X[j]		X[j]			X[r]		
Efficacy Measurements										
Tumor Imaging and RECIST assessment	X[p]		X[p]		X[p]		X[q]		X[p]	

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; however the treatment cycle interval may be increased due to toxicity according to the dose modification guidelines provided in Section 5.2.1.2. If the interval is increased, all procedures except imaging should be performed based on the new dosing schedule. 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. The first follow-up imaging assessment should occur 6 weeks (±7 days) from the last scheduled on-treatment imaging timepoint.
c. After the start of new anti-cancer treatment or documented disease progression by the central imaging vendor, whichever occurs first, the subject enters the Survival Follow Up Phase and should be contacted by telephone approximately every 12 weeks to assess for survival status. Updated survival status may be requested by the Sponsor at any time during the course of the study. Upon Sponsor notification, all subjects who do not/will not have a scheduled study visit or study contact during the Sponsor defined time period will be contacted for their survival status (excluding subjects that have a death event previously recorded).
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 from the first dose of Second Course treatment through 30 days after the last dose of Second Course treatment. 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 following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, 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.
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. PTT may be performed if the local lab is unable to perform aPTT.
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. 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 Second Course 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.
q. 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.
r. Unresolved labs that are drug related AEs should be followed until resolution. Labs do not need to be repeated after the end of trial treatment if labs are within normal range.

7.0 TRIAL PROCEDURES

7.1 Trial Procedures

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

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

7.1.1 Administrative Procedures

7.1.1.1 Informed Consent

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

7.1.1.1.1 General Informed Consent

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

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

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

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

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

7.1.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

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

7.1.1.2 Inclusion/Exclusion Criteria

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

7.1.1.3 Subject Identification Card

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

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

7.1.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee. Medical history will include all active conditions, and any condition diagnosed within the prior 10 years that are considered to be clinical significant by the Investigator. The subject's history of tobacco use will also be collected. 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 concomitant medication, if any, taken by the subject from the first dose of trial treatment through 30 days after the last dose of trial treatment. All medications related to reportable SAEs and ECIs should be recorded as defined in Section 7.2.

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.

For subjects randomized to either the pembrolizumab plus chemotherapy or standard treatment arm, investigators must choose which platinum drug will be used (carboplatin or cisplatin) prior to randomization. The selection will be documented in the trial database via IVRS/IWRS (See Data Entry 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 monitored by the investigator and/or institution 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 are 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 National Cancer Institute (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 in all treatment arms, all AEs of unknown etiology 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 regarding the identification, evaluation and management of potential irAEs.

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

7.1.2.2 Physical Exam

7.1.2.2.1 Full Physical Exam

The investigator or clinical designee will perform a complete physical exam during the screening period. Clinically significant abnormal findings should be recorded as medical history. Additional full physical exams 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 in a subject throughout the trial. CT scan is the more commonly used modality and is preferred for the majority of subjects. An MRI can be utilized if clinically appropriate.

Imaging should include the head, neck, chest, and abdomen at all timepoints specified in the Study Flow Chart. Imaging of the pelvis is optional. A CT from the vertex of the head to the thoracic inlet or a brain CT is strongly preferred. For an individual subject, imaging should be consistent at all timepoints, (i.e., follow-up scans should image the same areas as the baseline area, using the same imaging modality).

Local reading (investigator assessment with site radiology reading) based on RECIST 1.1 will be used to determine subject eligibility. Although RECIST 1.1 references a maximum of 5 target lesions in total and 2 per organ, Merck allows maximum of 10 target lesions in total and 5 per organ. 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.

The central imaging vendor will receive radiologic images for a retrospective analysis of subject eligibility and treatment response. **In addition, radiologic progression will be based on the independent central assessment of progression, rather than site assessment. The central imaging vendor will verify progressive disease (PD) following first radiologic evidence of PD assessed by the local site investigator. Verification of radiologic progression applies to all 3 treatment arms. 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 the date of randomization. The site study team must review pre-trial images to confirm the subject has measurable disease per RECIST 1.1.

Scans performed as part of routine clinical management are acceptable for use as the screening scan if they are of diagnostic quality and performed within 28 days prior to the date of 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 date of randomization. Subsequent imaging should be performed every 6 weeks (42 days ±7 days) or more frequently if clinically indicated. After 1 year, subjects who remain on treatment will have imaging performed every 9 weeks (±7 days). Imaging should not be delayed for delays in cycle starts.

Per RECIST 1.1, PR or CR 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 (i.e. 6 weeks later), whichever is clinically indicated. Imaging should then return to the original schedule beginning with the next protocol-specified timepoint.

Subjects who obtain a confirmation scan at 4 weeks do not need to undergo the next scheduled imaging assessment if it is due <4 weeks later; imaging may resume at the subsequent scheduled timepoint. (e.g. If a subject obtains a scan at Week 13 to confirm a Week 9 response, they will not be required to complete the scheduled Week 15 scan. The next imaging would then occur at Week 21 as usual).

Continue to perform imaging until whichever of the following occurs first:

- Initial site-assessed disease progression is verified by the central imaging vendor and confirmed by a repeat assessment ≥4 weeks later.

  Note: a repeat assessment is not required for subjects on the standard treatment arm.
- The start of new anti-cancer treatment
- Withdrawal of consent
- Death
- The end of the study

Note: For subjects on the pembrolizumab monotherapy or pembrolizumab plus chemotherapy arm, if the site-assessed disease progression is verified by the central imaging vendor and the subject is clinically stable as per section 7.1.2.6.3.1, it is the discretion of the PI to continue to treat and image the subject at least 4 weeks after the first scan indicating PD. irRECIST would then be followed by the site to determine if the follow-up scan confirms PD.

For subjects on the pembrolizumab monotherapy or pembrolizumab plus chemotherapy arms, confirmatory scans (at least 4 weeks after the first scan) will be submitted to the central imaging vendor; however the confirmatory scans do not need to be submitted for expedited Verification of Progression (VOP) unless progression was not verified on the scans showing initial site-assessed PD.

Subjects randomized to the standard treatment arm will not have irRECIST assessments.

Subjects who have unconfirmed disease progression may continue on treatment and follow the regular imaging schedule intervals 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). Scans showing site-assessed PD should be submitted to the central imaging vendor immediately. The site will be notified if the imaging vendor verifies disease progression using RECIST 1.1.

During the follow-up period, imaging will be repeated every 6 weeks (±7 days) during the first year of study participation and then every 9 weeks (±7 days) after 1 year. See the Trial Flow Charts in Section 6 and Section 7.1.5.3.2 for information about the Follow-up Visits.

7.1.2.6.3.1 irRECIST

As noted above for subjects on the pembrolizumab monotherapy or pembrolizumab plus chemotherapy arm, if site assessed PD has been verified by the central imaging vendor, the site may elect to continue treatment, repeat imaging ≥4 weeks later and assess tumor response or progression per irRECIST:

- If imaging shows PD, tumor assessment may be repeated by the site at least 4 weeks later in order to confirm PD with the option of continuing treatment for clinically stable subjects (see Table 13). Clinically stable is defined by the following criteria:
  - Absence of signs and symptoms indicating disease progression
  - No decline in ECOG PS
  - Absence of rapid progression of disease
  - Absence of progressive tumor at critical anatomical sites (e.g., cord compression) requiring urgent alternative medical intervention

Table 13 Imaging and Treatment After 1st Radiologic Evidence of PD

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

- In determining whether or not the tumor burden has increased or decreased, investigators should consider all target lesions as well as non-target lesions. Subjects that are deemed clinically unstable are not required to have repeat imaging for confirmation. If radiologic progression is confirmed by subsequent scan then the subject will be discontinued from trial treatment (exception noted in Section 7.1.2.6.3). If radiologic progression is not confirmed, then the subject should resume or continue trial treatment and have their next scan according to the protocol schedule of every 6 weeks (42 ± 7 days).

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

irRECIST data will be collected in the clinical database for subjects on the pembrolizumab monotherapy arm or the pembrolizumab plus chemotherapy arm.

irRECIST criteria are not applied to subjects on the standard treatment arm. After initial PD is verified by the central imaging vendor, subjects on the standard treatment arm will enter the Survival Follow-Up Phase.

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). HPV stratification in this trial may be performed using local testing of HPV status in subjects with oropharynx cancer using the specified method.

> Note: Tumor p16 expression must be evaluated by assessment of IHC analysis with CINtec® p16 Histology assay (Ventana Medical Systems Inc., Tucson AZ) using 'Benchmark Ultra' autostainer (Ventana, Tucson, AZ) 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: If local p16 testing results are not available, or cannot be assessed by the specified method, a tumor tissue sample may be submitted for p16 testing at the designated central laboratory.

All subjects will submit either a newly obtained (within 90 days prior to start of study treatment) or archival core or excisional biopsy (fine needle aspirate [FNA] is not adequate) to a central lab for characterization of PD-L1 status. A newly obtained biopsy is strongly preferred, but an archival sample is acceptable.

This specimen may be the diagnostic sample for subjects with a new diagnosis of metastatic HNSCC.

Tumor lesions used for newly obtained biopsies should not be the same lesions used as RECIST target lesions, unless there are no other lesions suitable for biopsy and following Sponsor consultation.

Blood for correlative studies (includes blood for DNA, RNA, and exploratory biomarkers) should be collected pre-dose at Cycle 1, Cycle 2, Cycle 3, and at treatment discontinuation. Blood for correlative samples (plasma and serum) will be collected pre-dose 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) and Pain Medication Log

The EuroQol EQ-5D, EORTC QLQ-C30, and EORTC QLQ-H&N35 questionnaires will be administered by trained site personnel and completed electronically by subjects in the following order: EuroQol EQ-5D first, then EORTC QLQ-C30, and lastly the EORTC QLQ-H&N35 at the time points specified in the Trial Flow Chart. It is a best practice and strongly recommended that ePROs are administered to randomized subjects prior to drug administration, AE evaluation, and disease status notification.

Subjects should complete the Pain Medication Log daily and return it to site personnel at each scheduled study visit as shown in the Trial Flow Chart. Site personnel will provide new Pain Medication Logs to the subjects as needed.

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 Section 2.3.

7.1.3.1 Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

Laboratory tests for hematology, chemistry and urinalysis are specified in Table 14.

Table 14 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[e]
WBC (total and differential)	Aspartate aminotransferase (AST)	Specific gravity	Total triiodothyronine (T3) or Free T3[b]
Red Blood Cell Count		Microscopic exam, if abnormal results are noted	Free thyroxine (T4)
Absolute Neutrophil Count	Calcium[c]	Urine pregnancy test[a]	Thyroid stimulating hormone (TSH)
Absolute Lymphocyte Count	Chloride		Blood for correlative studies
	Creatinine		PK (for subjects on the pembrolizumab arms)
	Glucose		Anti-pembrolizumab Antibodies (for subjects on the pembrolizumab arms)
	Magnesium		
	Phosphorus		
	Potassium		
	Sodium		
	Total Bilirubin		
	Direct Bilirubin, if total bilirubin is elevated above the upper limit of normal		
	Total protein		
	Blood Urea Nitrogen		
	A measure of carbon dioxide (CO_2 or bicarbonate)[b]		
	Uric acid		
	Urea[d]		

Hematology	Chemistry	Urinalysis	Other
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 available as standard of care in your region. The carbon dioxide may be either a measurement of CO_2 or bicarbonate as an electrolyte. c. Corrected calcium should be checked for subjects with hypoalbuminemia. d. Blood Urea Nitrogen is preferred; if not available urea may be tested. e. PTT may be performed if the local lab is unable to perform aPTT.			

Laboratory tests for screening should be performed within 10 days prior to the first dose of trial treatment. Screening labs should be collected and assessed prior to randomizing the subject. 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 (Section 6.1). Blood samples for PK and ADA collected may be stored only at this time. Further sample analysis may be performed 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 PK 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 be drawn from subjects in the pembrolizumab and pembrolizumab plus chemotherapy arms.

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 be drawn from subjects in the pembrolizumab and pembrolizumab plus chemotherapy arms.

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. 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). Subjects on the pembrolizumab monotherapy arm or pembrolizumab plus chemotherapy arm who discontinue treatment after they a) attain a CR or b) complete 24 months of treatment with pembrolizumab have the option of restarting treatment if they meet the criteria specified in Section 7.1.5.2.1.

7.1.4.1.1 Withdrawal From Future Biomedical Research

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

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

7.1.4.2 Blinding/Unblinding

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

7.1.4.3 Calibration of Critical Equipment

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

Critical Equipment for this trial includes:

- Laboratory equipment – as required for inclusion labs and trial assessments
- Imaging equipment – as required for study objectives
- Drug administration equipment – as required for storing, preparing, and administering study treatment

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

Within 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. ECOG must be 0 or 1 on the first day of dosing.
- 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.
- Tumor sample 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 90 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 monotherapy arm or pembrolizumab plus chemotherapy 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 2 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 and centrally-verified 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 180 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 180 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 for the second course phase are outlined in Section 6.2 – Trial Flow Chart – Second Course Phase – Retreatment with Pembrolizumab.

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 2 safety follow-up visits, 1 after the Treatment Period and 1 after the Second Course Phase.

7.1.5.3.2 Follow-up Visits

Subjects who discontinue trial treatment for a reason other than centrally-verified 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 determined by the central imaging vendor, 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.

For subjects who stopped treatment prior to the maximum time of 24 months due to confirmed CR or who completed 24 months of treatment, a less frequent imaging schedule of 12 weeks can be considered with Sponsor approval; this applies only to subjects prior to initiation of Second Course (retreatment).

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 which is verified by central review, and confirmed by the second radiologic assessment (confirmation scan applies to pembrolizumab arms only), or starts a new anticancer therapy, whichever occurs first, the subject enters the Survival Follow-Up Phase and should be contacted by telephone approximately every 12 weeks to assess for survival status 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 subjects who do not/will not have a scheduled study visit or study contact during the sponsor defined time period will be contacted for their survival status (excluding subjects that have 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).

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

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

For 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 an 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.

Cetuximab Overdose

There is no available information for the treatment of a cetuximab overdose. In cases of greater than recommended doses, the AEs were similar to the known safety profile. Appropriate supportive treatment should be provided if clinically indicated.

Otherwise, overdose should be managed according to local label and practice.

Carboplatin Overdose

There is no known antidote for carboplatin overdose. The anticipated complications of overdose may include myelosuppression and impairment of hepatic and renal function.

Otherwise, overdose should be managed according to local label and practice.

Cisplatin Overdose

There is no specific antidote for cisplatin overdose. Overdose may result in the side effects associated with the drug occurring in an excessive manner.

Otherwise, overdose should be managed according to local label and practice.

5-FU Overdose

Signs and symptoms of 5-FU overdose are similar to the adverse reactions associated with the drug and should be managed according to local label and practice. Subjects who have a 5-FU overdose should be closely monitored for 4 weeks.

Otherwise, overdose should be managed according to local label and practice.

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

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

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

7.2.2 Reporting of Pregnancy and Lactation to the Sponsor

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

Pregnancies and lactations that occur after the consent form is signed but before randomization 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 following cessation of Sponsor's product, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, must be reported by the investigator. All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

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

7.2.3 Immediate Reporting of Adverse Events to the Sponsor

7.2.3.1 Serious Adverse Events

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

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

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

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

Refer to Table 15 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 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, any ECI, or follow up to an ECI, whether or not related to the Sponsor's product, must be reported within 24 hours to the Sponsor, either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

Events of clinical interest for this trial include:

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

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

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

Subjects should be assessed for possible ECIs prior to each dose. 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. Any such event will be submitted to the Sponsor within 24 hours either by electronic or paper media.

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

The Sponsor will monitor unblinded aggregate 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 an 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. 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.

For studies in which multiple agents are administered as part of a combination regimen, the investigator may attribute each adverse event causality to the combination regimen or to a single agent of the combination. In general, causality attribution should be assigned to the combination regimen (i.e., to all agents in the regimen). However, causality attribution may be assigned to a single agent if in the investigator's opinion, there is sufficient data to support full attribution of the adverse experience to the single agent.

Table 15 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 8.1.4 - 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, 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, but prior to the conduct of any interim analysis for

efficacy, will be documented in a supplemental SAP (sSAP) and referenced in the Clinical Study Report (CSR) for the study. Post hoc exploratory analyses will be clearly identified in the CSR. The PRO analysis plan will also be included in the sSAP.

In addition, a separate analysis plan document will be issued prior to the conduct of any interim analysis for efficacy for the following:

- Pharmacokinetics and pharmacodynamics evaluation (detailed in Section 7.1.3.2).

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 Analysis

The primary and key secondary or exploratory endpoints, primary analysis population, and statistical methods that will be employed for the efficacy analyses are presented in Table 20.

The intention-to-treat (ITT) population that includes all randomized subjects will serve as the primary population for the analyses of efficacy data in this trial. Regular safety monitoring is planned in this trial (Section 8.2.9). If, upon the recommendation of DMC, the enrollment in pembrolizumab in combination with chemotherapy arm is paused and re-opened, subjects randomized during the pause will be excluded from the efficacy analysis population of pembrolizumab in combination with chemotherapy vs. standard treatment comparisons.

The primary efficacy endpoints are:

- PFS per RECIST 1.1 (i.e., time from randomization to documented progressive disease or death due to any cause, whichever occurs first)
- OS (i.e., time from randomization to death due to any cause)

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 population will be employed for safety analyses. For this study, there are no pre-specified events of interest, i.e., no Tier 1 events.

8.1.3 Power and Sample Size

The study plans to randomize approximately 825 subjects with 1:1:1 ratio into the treatment groups of pembrolizumab monotherapy, a combination of pembrolizumab with chemotherapy and standard treatment, stratified by PD-L1 expression (strongly positive vs. not strongly positive as defined by TPS 50% cutpoint), HPV status (HPV+ vs. HPV-), and ECOG performance status (0 vs. 1). The prevalence of the PD-L1 positive sub-population is projected to be 50% for PD-L1 CPS 20 and 80% for PD-L1 CPS 1 subpopulation.

Two interim efficacy analyses are planned in this study. A Hwang-Shih-DeCani alpha-spending function with gamma parameter [redacted] is constructed to implement group

sequential efficacy boundaries to control the Type I error for each PFS and each OS hypothesis.

PFS

Two PFS analyses are planned at interim analyses 1 and 2. The PFS hypotheses will be tested at interim analysis 1, and a second test of PFS, which will be the final PFS analyses, may occur at interim analysis 2 only if superior PFS is not declared at interim analysis 1. At the time of final PFS analysis,

H1, H4: for subjects with PD-L1 CPS 20, it is expected that approximately 237 PFS events will have been observed between one experimental treatment and standard treatment. The study has 90% power with each experimental treatment (pembrolizumab monotherapy [H1] or pembrolizumab in combination with chemotherapy [H4]) to detect a hazard ratio of 0.58 vs. standard treatment at alpha = 0.19% (one-sided).

H2, H5: for subjects with PD-L1 CPS 1, it is expected that approximately 378 PFS events will have been observed between one experimental treatment and standard treatment. The study has 98.6% power with each experimental treatment (pembrolizumab monotherapy [H2] or pembrolizumab in combination with chemotherapy [H5]) to detect a hazard ratio of 0.59 vs. standard treatment at alpha = 0.19% (one-sided). (Note that H2 will be tested only if H1 is rejected and H5 will be tested only if H4 is rejected)

H3: for all subjects, it is expected that approximately 474 PFS events will have been observed between pembrolizumab monotherapy and standard treatment. The study has 99.6% power with pembrolizumab monotherapy to detect a hazard ratio of 0.6 vs. standard treatment at alpha = 0.19% (one-sided). (Note that H3 will be tested only if H1 and H2 are rejected under the multiplicity strategy.)

H6: for all subjects, it is expected that approximately 474 PFS events will have been observed between pembrolizumab in combination with chemotherapy and standard treatment. The study has 97.7% power with pembrolizumab in combination with chemotherapy to detect a hazard ratio of 0.6 vs. standard treatment at alpha = 0.02% (one-sided).

The PFS sample size calculation is based on the following assumptions: 1) progression-free survival follows an exponential distribution with a median of 6 months in the standard treatment arm; 2) hazard ratios are 0.58 for subjects with PD-L1 CPS 20, 0.59 for subjects with PD-L1 CPS 1 and 0.6 for all subjects; 3) an enrollment period of 21 months; 4) at least 9 months follow-up at interim analysis 1, and 17 months follow-up at interim analysis 2; and 5) a yearly dropout rate of 5%.

OS

Three OS analyses are planned at interim analyses 1, 2 and the final analysis. At the time of the final analysis:

H7, H11: for subjects with PD-L1 CPS 20, it is expected that approximately [redacted] deaths will have been observed between one experimental treatment and standard treatment. The study has 90.5% power with each experimental treatment (pembrolizumab monotherapy [H7] or pembrolizumab in combination with chemotherapy [H11]) to detect a hazard ratio of 0.6 vs. standard treatment at alpha = 0.7% (one-sided).

H8, H12: for subjects with PD-L1 CPS 1, it is expected that approximately [redacted] deaths will have been observed between one experimental treatment and standard treatment. The study has 94.3% power with each experimental treatment (pembrolizumab monotherapy [H8] or pembrolizumab in combination with chemotherapy [H12]) to detect a hazard ratio of 0.65 vs. standard treatment at alpha = 0.7% (one-sided). (Note that H8 will be tested only if H7 is rejected and H12 will be tested only if H11 is rejected.)

H9, H13: for all subjects, it is expected that approximately [redacted] deaths will have been observed between one experimental treatment and standard treatment. The study has 87.85% power with a hazard ratio of 0.85 to establish non-inferiority (NI margin = 1.2) for each experimental treatment (pembrolizumab monotherapy [H9] or pembrolizumab in combination with chemotherapy [H13]) vs. standard treatment at alpha = 0.7% (one-sided). (Note that H9 will be tested only if H7 and H8 are rejected under the multiplicity strategy.)

H10, H14: for all subjects, it is expected that approximately [redacted] deaths will have been observed between one experimental treatment and standard treatment. The study has 90.4% power with each experimental treatment (pembrolizumab monotherapy [H10] or pembrolizumab in combination with chemotherapy [H14]) to detect a hazard ratio of 0.7 vs. standard treatment at alpha = 0.7% (one-sided). (Note that H10 will be tested only if H7 through H9 are rejected under the multiplicity strategy and H14 will be tested only if non-inferiority is established for H13.)

The OS sample size calculation is based on the following assumptions: 1) overall survival follows an exponential distribution with a median of 10 months in the standard treatment arm; 2) the hazard ratios are 0.6 for subjects with PD-L1 CPS 20, 0.65 for subjects with PD-L1 CPS 1, 0.7 for all subjects for the superiority hypotheses, and 0.85 for all subjects for the non-inferiority hypotheses; 3) an enrollment period of 21 months; 4) at least [redacted] follow-up; and 5) a yearly dropout rate of 2%.

The assumptions for median PFS of 6 months and median OS of 10 months in the standard treatment arm is based on the median PFS and median OS estimates from the EXTREME trial [40; 54]. The assumptions do not take into account potential prognostic implications in a biomarker selected population. As such, the median of the standard treatment arm for the PD-L1 positive subgroups may be more or less than 6 months for PFS and more or less than 10 months for OS.

8.1.4 Interim Analyses

Two efficacy interim analyses, one formal safety interim analysis and quarterly safety monitoring will be performed in this study. Results will be reviewed by an external DMC. These interim analyses are summarized below. Details are provided in Section 8.2.9.

8.1.4.1 Safety Interim Analyses

The endpoints, timing and purpose of the safety interim analysis are summarized in Table 16 below. The decision rule and other statistical details are further described in Section 8.2.9.

Table 16 Summary of Interim Safety Analysis Strategy

Key Endpoints for Interim Analysis	Timing of Interim Analysis	Purpose of Interim Analysis
• Percentage of subjects who require a dose modification • AE data	• 10 subjects in the pembrolizumab in combination with chemotherapy arm have completed 2 cycles of treatment • quarterly	• Safety evaluation

8.1.4.2 Efficacy Interim Analyses

There will be two interim analyses for efficacy. Table 17 below summarizes the analysis strategies. Further details of interim analyses are provided in Section 8.2.9 as well as in the DMC charter.

Table 17 Summary of PFS and OS Analysis Strategies

PFS and OS Analyses	Key Endpoints	Timing of Analysis	Expected Number of Events at the Time of Analysis	Primary Purpose of Analysis
Interim analysis 1	• PFS • OS	30 months from study start	• ~423 PFS events between pembrolizumab in combination with chemotherapy and standard treatment in all subjects	• Demonstrate PFS and OS superiority
Interim analysis 2	• OS	38 months from study start	• ~421 deaths between pembrolizumab in combination with chemotherapy and standard treatment in all subjects	• Demonstrate PFS (if not significant at IA1) and OS superiority
Final analysis	• OS	[redacted] from study start	• [redacted] between one experimental treatment and standard treatment in PD-L1 CPS 20 • [redacted] between one experimental treatment and standard treatment in PD-L1 CPS 1 • [redacted] between one experimental treatment and standard treatment in all subjects	• Demonstrate OS superiority
For the interim analyses, the actual timing is determined by the minimum follow-up; and for the final analysis, [redacted] The table only lists the timing and the expected event numbers of the hypotheses that drive the analysis. The event numbers of other hypotheses are provided in Section 8.2.9.2.				

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 randomized allocation schedule will be generated and implemented by the vendor of the study interactive voice response system (IVRS).

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

The investigator and 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 Sponsor statistician, unblinded Sponsor statistical programmer, and unblinded data manager will have access to the subject-level PD-L1 results for the purpose of data review and will have no other responsibilities associated with the study. 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. Key enrollment metrics and study data will also be monitored by the unblinded Sponsor statistician and unblinded Sponsor statistical programmer to inform the timing of each analysis.

Planned interim analyses are described in Section 8.2.9. The PFS analyses, described in Section 8.2.9, occurs prior to the final OS analysis. Treatment-level results at the interim analyses will be provided by the external unblinded statistician to the eDMC. The DMC will serve as the primary reviewer of the results of the interim analyses, and will make recommendations for discontinuation of the study or modification to the Sponsor Executive Oversight Committee. Depending on the recommendation of the external DMC, the Sponsor may prepare a regulatory submission. Participant-level unblinding to support regulatory filing will be restricted to a designate team in the Sponsor, who will have no other responsibilities associated with the study. If the DMC recommends modifications to the design of the protocol or discontinuation of the study, the executive oversight committee may be unblinded to results at the treatment level in order to act on these recommendations. Additional logistical details, revisions to the above plan, 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 Sponsor and external unblinded statisticians will not be involved in any discussions regarding modifications to the protocol, statistical methods, identification of protocol deviations, or data validation efforts after the interim analyses.

8.2.2 Hypotheses/Estimation

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

8.2.3 Analysis Endpoints

Efficacy and safety endpoints that will be evaluated are listed below.

8.2.3.1 Efficacy Endpoints

Primary

Progression-free survival (PFS) – RECIST 1.1 by BICR

Progression-free-survival is defined as the time from randomization to the first documented disease progression per RECIST 1.1 based on BICR or death due to any cause, whichever occurs first. See Section 8.2.5.1.1 for definition of censoring.

Overall Survival

Overall Survival 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

Proportion progression free at 6 months and 12 months – RECIST 1.1 by BICR

The proportion progression free at 6 months and at 12 months is defined as the Kaplan-Meier estimate of the survival function for PFS at 6 months and 12 months, respectively. The progression-free status is based upon BICR per RECIST 1.1.

Objective Response Rate (ORR) – RECIST 1.1 by BICR

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 BICR per RECIST 1.1.

Exploratory

Duration of Response (DOR) – RECIST 1.1 by BICR

For subjects who demonstrated CR or PR, duration of response is defined as the time from first documented evidence of CR or PR until disease progression or death, whichever occurs first.

Details of other exploratory endpoints will be provided in the sSAP.

8.2.3.2 Safety Endpoints

Safety measurements are described in Section 7 Trial Procedures.

8.2.3.3 PRO Endpoints

Global health status/quality of life assessment is based on the global health status/quality of life scales of the QLQ-C30 (items 29 and 30); pain is based on the pain multi-item scales of the EORTC QLQ-H&N35 (items 31-34), and TTD in swallowing is based on the swallowing multi-item scales of the EORTC QLQ-H&N35 (items 35-38).

TTD is defined as the time from baseline to first onset of PRO deterioration with confirmation (true deterioration). Here, true deterioration in the global health status/quality of life, pain, and swallowing endpoints is defined as a 10 points or greater worsening from baseline for each multi-item scale [48; 52; 53] and confirmed by a second adjacent 10 or more deterioration from baseline under a right-censoring rule.

8.2.4 Analysis Populations

8.2.4.1 Efficacy Analysis Populations

The analysis of primary efficacy endpoints are based on the ITT population, i.e., subjects will be included in the treatment group to which they are randomized. If, upon the recommendation of DMC, the enrollment in pembrolizumab in combination with chemotherapy arm is paused and re-opened, subjects randomized during the pause will be

excluded from the efficacy analysis population of pembrolizumab in combination with chemotherapy vs. standard treatment comparisons. Details on the approach to handling missing data are provided in Section 8.2.5 Statistical Methods.

8.2.4.2 Safety Analysis Populations

The All Subjects as Treated (ASaT) population will be used for the analysis of safety data in this study. The ASaT population consists of all randomized subjects who received at least one dose of study treatment. Subjects will be included in the treatment group corresponding to the study treatment they actually received for the analysis of safety data using the ASaT population. 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 study treatment is required for inclusion in the analysis of each specific parameter. To assess change from baseline, a baseline measurement is also required.

8.2.4.3 PRO Analysis Population

The PRO analyses are based on the PRO full analysis set (FAS) population, defined as subjects who have at least one PRO assessment available and have received at least one dose of the study medication.

8.2.5 Statistical Methods

This section describes the statistical methods that primarily address the primary and secondary objectives. Methods related to exploratory objectives will be described in the sSAP.

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

8.2.5.1 Statistical Methods for Efficacy Analyses

8.2.5.1.1 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% CI 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 used as the stratification

factors in both the stratified log-rank test and the stratified Cox model for the analyses in all subjects and in subjects with PD-L1 CPS 1. For analyses in the PD-L1 CPS 20 subgroup, HPV status and ECOG status will be used as the stratification factors. In the event that there are low event counts (<5) in one or more strata, for the analysis purpose, strata will be combined to ensure sufficient number of events in each stratum. The order of stratification factors to combine strata over is as follows:

1. Eliminate ECOG performance score from analysis stratification, leaving stratification by PD-L1 tumor expression defined by TPS and HPV status;
2. Eliminate both ECOG performance score and HPV status from analysis stratification, leaving stratification by PD-L1 tumor expression defined by TPS;
3. Eliminate all stratification factors.

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 investigator's assessment.

In order to evaluate the robustness of the PFS endpoint per RECIST 1.1 by central imaging vendor, we will perform 2 sensitivity analyses with a different set of censoring rules. The first sensitivity analysis is the same as the primary analysis except that data for any subject who misses more than one disease assessment (with or without a subsequent death or progression) are censored at the last disease assessment prior to missing visits. The second sensitivity analysis is the same as the primary analysis except that it considers discontinuation of treatment or initiation of an anticancer treatment subsequent to discontinuation of study-specified treatments, whichever occurs later, to be a PD event for subjects without documented PD or death. If a subject meets multiple criteria for censoring, the censoring criterion that occurs earliest will be applied. The censoring rules for primary and sensitivity analyses are summarized in Table 18.

Table 18 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
No PD and no death; ≥ 2 consecutive missed disease assessments	Censored at last disease assessment	Censored at last disease assessment prior to ≥2 consecutive missed visits	Censored at last disease assessment
PD or death documented after ≤ 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 at any time after ≥ 2 missed disease assessments	Progressed at date of documented PD or death	Censored at last disease assessment prior to the ≥ 2 missed disease assessment	Progressed at date of documented PD or death

8.2.5.1.2 Overall Survival (OS)

The non-parametric Kaplan-Meier method will be used to estimate the survival curve**s**. 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% CI 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 used as the stratification factors in both the stratified log-rank test and the stratified Cox model for the analyses in all subjects and in subjects with PD-L1 CPS 1. For analyses in the PD-L1 CPS 20 subgroup, HPV status and ECOG status will be used as the stratification factors. In the event that there are low event counts (<5) in one or more strata, for the analysis purpose, strata will be combined to ensure sufficient number of events in each stratum. The order of stratification factors to combine strata over is the same as specified for PFS analysis.

Since subjects in the standard therapy arm are expected to discontinue treatment earlier compared to subjects in the pembrolizumab arms, and they may switch to another anti PD-1 treatment following confirmation of progressive disease, adjustment for the effect of crossover on OS may be performed based on recognized methods, e.g. the Rank Preserving

Structural Failure Time (RPSFT) model proposed by Robins and Tsiatis (1989) [55], two stage model, etc., based on an examination of the appropriateness of the data to the assumptions required by the methods.

8.2.5.1.3 Proportion Progression Free at 6 months and 12 months

Kaplan-Meier estimates of the survival function for PFS at 6 months and 12 months will be provided by treatment group. Confidence intervals for the difference between the treatment groups (pembrolizumab vs. standard treatment or a combination of pembrolizumab with chemotherapy vs. standard treatment) will be constructed using standard methods.

8.2.5.1.4 Objective Response Rate (ORR)

The stratified Miettinen and Nurminen's method will be used for comparison of the objective response rates between the treatment groups. The difference in ORR and its 95% CI from the stratified Miettinen and Nurminen method with strata weighting by sample size will be provided. The same stratification factors used for randomization (see Section 5.4) will be used as the stratification factors in the analysis of all subjects and subjects with PD-L1 CPS 1. For analyses in the PD-L1 CPS 20 subgroup, HPV status and ECOG status will be used as the stratification factors. In the event that there are low responses (<5) in one or more strata, for the analysis purpose, strata will be combined to ensure sufficient number of responses in each stratum. The order of stratification factors to combine strata over is the same as specified for PFS analysis. Sensitivity analyses will be performed for comparison of ORR based on investigator's assessment.

8.2.5.1.5 Duration of Response (DOR)

For subjects who demonstrate CR or PR, DOR is defined as the time from first documented evidence of CR or PR until disease progression or death due to any cause, whichever occurs first. Censoring rules for DOR are summarized in Table 19. DOR will be assessed using RECIST 1.1 separately by BICR and by investigator's assessment.

For each DOR analysis, a corresponding summary of the reasons responding subjects are censored will also be provided. Subjects who are alive, have not progressed, have not initiated new anti-cancer treatment, have not been determined to be lost to follow-up, and have had a disease assessment within ~5 months of the data cutoff date are considered ongoing responders at the time of analysis. If a subject meets multiple criteria for censoring, the censoring criterion that occurs earliest will be applied.

Table 19 Censoring Rules for DOR

Situation	Date of Progression or Censoring	Outcome
No progression nor death, no new anti-cancer therapy initiated	Last adequate disease assessment	Censor (non-event)
No progression nor death, new anti-cancer therapy initiated	Last adequate disease assessment before new anti-cancer therapy initiated	Censor (non-event)
Death or progression after ≥2 consecutive missed disease assessments	Last adequate disease assessment prior to the ≥ 2 missed adequate disease assessments	Censor (non-event)
Death or progression after ≤ 1 missed adequate disease assessments	PD or death	End of response (Event)
A missed disease assessment includes any assessment that is not obtained or is considered inadequate for evaluation of response.		

8.2.5.1.6 Summary of Efficacy Analysis Methods

A summary of the primary analysis strategy for the primary and secondary efficacy endpoints is provided in Table 20.

Table 20 Efficacy Analysis Methods for Primary and Secondary Efficacy Endpoints

Endpoint/Variable (Description, Time Point)	Statistical Method	Analysis Population	Missing Data Approach
Primary Analyses:			
PFS (RECIST 1.1) by BICR	Testing: Stratified Log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT • All subjects • Subjects with PD-L1 CPS 20 and CPS 1	Censored according to rules in Table 18
OS	Testing: Stratified Log-rank test (for superiority hypotheses only) Estimation: Stratified Cox model with Efron's tie handling method	ITT • All subjects • Subjects with PD-L1 CPS 20 and CPS 1	Censored at last known alive date

Endpoint/Variable (Description, Time Point)	Statistical Method	Analysis Population	Missing Data Approach
Secondary Analyses:			
PFS at 6 months/12 months (RECIST 1.1) by BICR	Kaplan-Meier estimation with CI	ITT • All subjects • Subjects with PD-L1 CPS 20 and CPS 1	Censored according to primary censoring rule in Table 18
ORR (RECIST 1.1) by BICR	Stratified Miettinen and Nurminen method	ITT • All subjects • Subjects with PD-L1 CPS 20 and CPS 1	Subjects with missing data are considered non-responders
Exploratory Analyses:			
DOR (RECIST 1.1) by BICR	Summary statistics using Kaplan-Meier method	All responders in ITT	Non-responders are excluded in analysis
Sensitivity analyses will be performed for PFS, ORR and DOR based on investigator's assessment.			

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.

The analysis of safety results will follow a tiered approach (Table 21). 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. Adverse experiences (specific terms as well as system organ class terms), consisting of the percentage of subjects with any AE, any drug related AE, any Grade 3-5 AE, any serious AE, any AE which is both drug-related and Grade 3-5, any AE which is both serious and drug-related, dose modification due to AE, and who discontinued due to an AE, and death 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 will belong to Tier 3.

Table 21 Analysis Strategy for Safety Parameters

Safety Tier	Safety Endpoint	p-Value	95% CI for Treatment Comparison	Descriptive Statistics
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

8.2.5.3 Statistical Methods for PRO Analyses

The Kaplan-Meier method will be used to estimate the TTD survival curve for each of the global health status/quality of life, pain and swallowing outcomes in each treatment group. A stratified Cox proportional hazard (PH) model with Efron's method of tie handling will be used to assess the magnitude of the treatment difference. Stratification factors used for randomization will be used in the stratified Cox PH model. The hazard ratio, 95% confidence interval, and nominal p-value will be reported.

To assess the treatment effects on the PRO score changes from baseline in the global health status/quality of life outcome, a constrained longitudinal data analysis (cLDA) model will be applied, with the PRO score as the response variable, and treatment by time interaction, and stratification factors as covariates. Treatment effect on PRO score change from baseline will be primarily evaluated at Week 15. The differences in the least square mean change from baseline will be reported at the primary analysis time point.

8.2.5.4 Summaries of Baseline Characteristics and Demographics

The comparability of the treatment groups for each relevant characteristic will be assessed by the use of tables and/or graphs in all subjects as well as in subjects with PD-L1 positive expression. 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 overall type I error rate is strongly controlled at 2.5% (one-sided) with:

- 0.19% allocated to each PFS hypothesis of pembrolizumab monotherapy vs. standard treatment (H1) and pembrolizumab in combination with chemotherapy vs. standard treatment (H4) in subjects with PD-L1 CPS 20;
- 0.02% allocated to PFS hypothesis of pembrolizumab in combination with chemotherapy vs. standard treatment in all subjects (H6);
- 0.7% allocated to each OS hypothesis of pembrolizumab monotherapy vs. standard treatment (H7) and pembrolizumab in combination with chemotherapy vs. standard treatment (H11) in subjects with PD-L1 CPS 20;
- 0.7% allocated to OS non-inferiority hypothesis of pembrolizumab in combination with chemotherapy vs. standard treatment in all subjects (H13).

For the PFS hypotheses of pembrolizumab monotherapy vs. standard treatment, a fixed sequential testing will be applied in the order of PFS superiority in subjects with PD-L1 CPS 20 (H1), in subjects with PD-L1 CPS 1 (H2), and in all subjects (H3).

For the PFS hypotheses of pembrolizumab in combination with chemotherapy vs. standard treatment, a fixed sequential testing will be applied in the order of PFS superiority in subjects with PD-L1 CPS 20 (H4) and in subjects with PD-L1 CPS 1 (H5). If H5 is rejected, then the corresponding alpha will be fully shifted to PFS superiority hypothesis for all subjects (H6).

If any of the PFS null hypotheses in all subjects (H3 and H6) is rejected, the corresponding alpha level will be shifted and distributed to the OS hypotheses for the corresponding experimental treatment using the graphical approach of Maurer and Bretz (2013) [57].

For the OS hypotheses of pembrolizumab monotherapy vs. standard treatment, a fixed sequential testing will be applied in the order of OS superiority in subjects with PD-L1 CPS 20 (H7), OS superiority in subjects with PD-L1 CPS 1 (H8), OS non-inferiority in all subjects (H9) and OS superiority in all subjects (H10). If H10 is rejected, then the corresponding alpha will be essentially fully reallocated and distributed equally to H11 and H13 if not already significant, with a very small fraction (0.002) reallocated to H1.

For the OS hypotheses of pembrolizumab in combination with chemotherapy vs. standard treatment, a fixed sequential testing will be applied in the order of OS superiority in subjects with PD-L1 CPS 20 (H11) and OS superiority in subjects with PD-L1 CPS 1 (H12). If H12 is significant, the corresponding alpha will be shifted fully to OS non-inferiority in all subjects (H13). If H14 is rejected, then the corresponding alpha will be essentially fully reallocated to H7 if not already significant, with a very small fraction (0.001) reallocated to H4.

The alpha reallocation strategy will follow the graphical approach of Maurer and Bretz (2013) [57]. [redacted]

Figure 3 displays the multiplicity strategy diagram for the study.

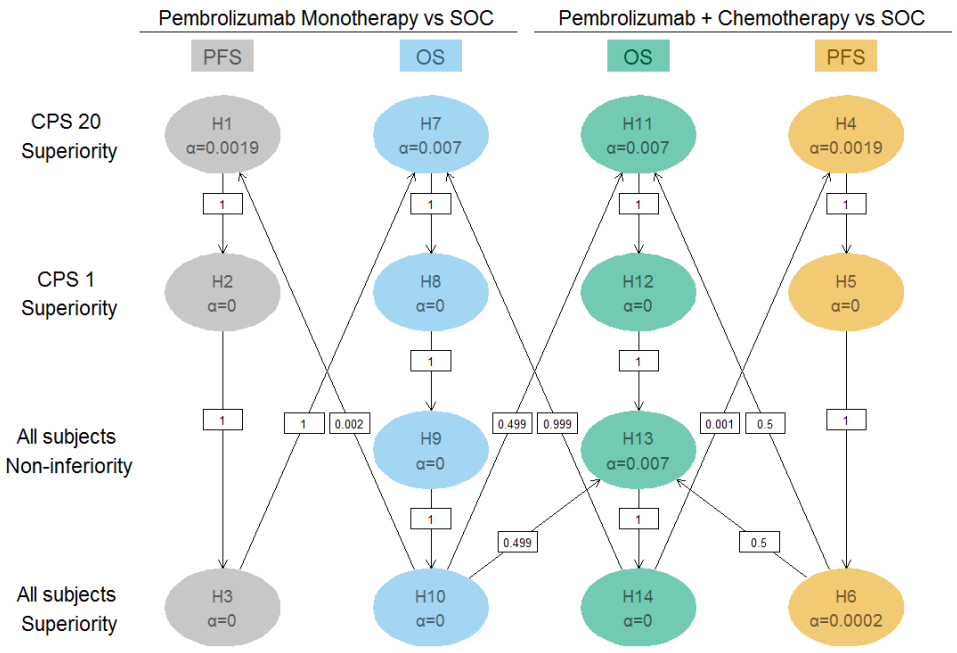


Figure 3 Multiplicity Strategy

8.2.7 Sample Size and Power Calculation

The study plans to randomize approximately 825 subjects with 1:1:1 ratio into the treatment groups of pembrolizumab monotherapy, a combination of pembrolizumab with chemotherapy and standard treatment, stratified by PD-L1 expression (strongly positive vs. not strongly positive), HPV status (HPV+ vs. HPV-), and ECOG performance status (0 vs. 1). The prevalence of PD-L1 positive sub-population is projected to be 50% for PD-L1 CPS 20 and 80% for the PD-L1 CPS 1 sub-population.

Two interim efficacy analyses are planned in this study. A Hwang-Shih-DeCani alpha-spending function with gamma parameter [redacted] is constructed to implement group sequential efficacy boundaries for each PFS and each OS hypothesis.

PFS:

Two PFS analyses are planned at interim analyses 1 and 2. The PFS hypotheses will be tested at interim analysis 1, and a second test of PFS, which will be the final PFS analyses, may occur at interim analysis 2 only if superior PFS is not declared at interim analysis 1. At the time of the final PFS analysis:

H1, H4: for subjects with PD-L1 CPS 20, it is expected that approximately 237 PFS events will have been observed between one experimental treatment and standard treatment. The study has 90% power with each experimental treatment (pembrolizumab monotherapy [H1] or pembrolizumab in combination with chemotherapy [H4]) to detect a hazard ratio of 0.58 vs. standard treatment at alpha = 0.19% (one-sided).

H2, H5: for subjects with PD-L1 CPS 1, it is expected that approximately 378 PFS events will have been observed between one experimental treatment and standard treatment. The study has 98.6% power with each experimental treatment (pembrolizumab monotherapy [H2] or pembrolizumab in combination with chemotherapy [H5]) to detect a hazard ratio of 0.59 vs. standard treatment at alpha = 0.19% (one-sided). (Note that H2 will be tested only if H1 is rejected and H5 will be tested only if H4 is rejected.)

H3: for all subjects: it is expected that approximately 474 PFS events will have been observed between pembrolizumab monotherapy and standard treatment. The study has 99.6% power with pembrolizumab monotherapy to detect a hazard ratio of 0.6 vs. standard treatment at alpha = 0.19% (one-sided). (Note that H3 will be tested only if H1 and H2 are rejected under the multiplicity strategy.)

H6: for all subjects, it is it is expected that approximately 474 PFS events will have been observed between pembrolizumab in combination with chemotherapy and standard treatment. The study has 97.7% power with pembrolizumab in combination with chemotherapy to detect a hazard ratio of 0.6 vs. standard treatment at alpha = 0.02% (one-sided).

The PFS sample size calculation is based on the following assumptions: 1) progression-free survival follows an exponential distribution with a median of 6 months in the standard treatment arm; 2) hazard ratios are 0.58 for subjects with PD-L1 CPS 20, 0.59 for subjects with PD-L1 CPS 1 and 0.6 for all subjects; 3) an enrollment period of 21 months; 4) at least 9 months follow-up at interim analysis 1, and 17 months follow-up at interim analysis 2; and 5) a yearly dropout rate of 5%.

OS

Three OS analyses are planned at interim analyses 1, 2 and the final analysis. At the time of the final analysis:

H7, H11: for subjects with PD-L1 CPS 20, it is expected that approximately [redacted] deaths will have been observed between one experimental treatment and standard treatment. The study has 90.5% power with each experimental treatment (pembrolizumab monotherapy [H7] or pembrolizumab in combination with chemotherapy [H11]) to detect a hazard ratio of 0.6 vs. standard treatment at alpha = 0.7% (one-sided).

H8, H12: for subjects with PD-L1 CPS 1, it is expected that approximately [redacted] deaths will have been observed between one experimental treatment and standard treatment. The study has 94.3% power with each experimental treatment (pembrolizumab monotherapy [H8] or pembrolizumab in combination with chemotherapy [H12]) to detect a hazard ratio of 0.65 vs. standard treatment at alpha = 0.7% (one-sided). (Note that H8 will be tested only if H7 is rejected and H12 will be tested only if H11 is rejected.)

H9, H13: for all subjects, it is expected that approximately [redacted] deaths will have been observed between one experimental treatment and standard treatment. The study has 87.85% power with a hazard ratio of 0.85 to establish non-inferiority (NI margin = 1.2) for each experimental treatment (pembrolizumab monotherapy [H9] or pembrolizumab in combination with chemotherapy [H13]) vs. standard treatment at alpha = 0.7% (one-sided). (Note that H9 will be tested only if H7 and H8 are rejected under the multiplicity strategy.)

H10, H14: for all subjects, it is expected that approximately [redacted] deaths will have been observed between one experimental treatment and standard treatment. The study has 90.4% power with each experimental treatment (pembrolizumab monotherapy [H10] or pembrolizumab in combination with chemotherapy [H14]) to detect a hazard ratio of 0.7 vs. standard treatment at alpha = 0.7% (one-sided). (Note that H10 will be tested only if H7 through H9 are rejected under the multiplicity strategy and H14 will be tested only if non-inferiority is established for H13.)

The OS sample size calculation is based on the following assumptions: 1) overall survival follows an exponential distribution with a median of 10 months in the standard treatment arm; 2) the hazard ratios are 0.6 for subjects with PD-L1 CPS 20, 0.65 for subjects with PD-L1 CPS 1, 0.7 for all subjects for the superiority hypotheses, and 0.85 for all subjects for the non-inferiority hypotheses; 3) an enrollment period of 21 months; 4) at least [redacted] follow-up; and 5) a yearly dropout rate of 2%.

The assumptions for median PFS of 6 months and median OS of 10 months in the standard treatment arm are based on median PFS and median OS estimates from the EXTREME trial [40; 54]. The assumptions do not take into account potential prognostic implications in a biomarker selected population. As such, the median of the standard treatment for the PD-L1 positive subgroup may be more or less than 6 months for PFS, and more or less than 10 months for OS.

The sample size and power calculations were performed in the software EAST 6 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 by treatment group within each category of the following classification variables:

- Stratification factors
  - PD-L1 subgroup (strongly positive vs. not strongly positive, defined by TPS 50%)
  - HPV status (HPV positive vs. HPV negative)
  - ECOG status (0 vs. 1)
- PD-L1 expression level defined by CPS (≥ 20 vs. not ≥ 20; and ≥ 1 vs. not ≥ 1)
- Age category (<65 vs. ≥65 years)
- Sex (female vs. male)
- Race (white vs. non-white)
- Region (North America [NA] vs European Union [EU] vs Rest of the World [ROW])
- Smoking status (never vs. former vs. current)
- Disease status (recurrent vs. metastatic)

In addition, a Forest plot will be produced, which provides the estimated point estimates and confidence intervals for the treatment effect across the categories of subgroups listed above.

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 Analyses

8.2.9.1 Safety Interim Analyses

A formal interim safety analysis will take place after 10 subjects in pembrolizumab in combination with chemotherapy arm have completed 2 cycles of therapy. If the majority of the enrolled subjects (more than 80%) require a dose modification of platinum and/or 5-FU by the end of the 2nd cycle, the dose of the chemotherapies may be reduced for the remainder

of the study. If the majority of the participants (more than 80%) require 2 dose modifications of platinum and/or 5-FU by the end of the 2nd cycle, the SPONSOR may consider discontinuing the combination arm.

Table 22 below summarizes the probabilities of observing the numbers and percentages of subjects who require 1 dose modification under different assumptions of true dose modification rate θ_0, which can be interpreted as the p-values for testing the null hypothesis that the true dose modification rate is less than θ_0. These criteria are considered non-binding guidelines, i.e., a recommendation would not be based solely on statistical grounds, as many other factors (i.e., all aspects of the data from the trial) may be part of the decision process.

Additionally, safety monitoring interim analyses are planned to be conducted approximately every quarter and will commence following the completion of the formal planned safety interim analysis. The number of percentage of subjects with a dose modification, together with AE data, will be summarized. Additional details of the monitoring timing and guidelines will be provided in the DMC charter.

Table 22 Probability of Observing the Number (%) of Subjects who Require a Dose Modification

Observed number (%) of subjects	Probabilities (p-values) under different assumptions				
	$\theta_0 = 0.5$	$\theta_0 = 0.6$	$\theta_0 = 0.7$	$\theta_0 = 0.8$	$\theta_0 = 0.9$
5 (50.0%)	0.377	0.633	0.850	0.967	0.998
6 (60.0%)	0.172	0.382	0.650	0.879	0.987
7 (70.0%)	0.055	0.167	0.383	0.678	0.930
8 (80.0%)	**0.011**	**0.046**	0.149	0.376	0.736
9 (90.0%)	**0.001**	**0.006**	**0.028**	0.107	0.349

The probabilities (p-values) for the monitoring of the first 10 subjects who have completed 2 cycles of therapy were calculated from Binomial distribution; and for the quarterly safety monitoring, the probabilities (p-values) can be calculated from asymptotical Normal distribution based on the observed proportion of subjects with a dose modification and the number of subjects at the time of analysis.

8.2.9.2 Efficacy Interim Analyses

Two interim analyses are currently planned. Results will be reviewed by an external data monitoring committee (DMC). Further details of interim analyses are provided below and will be incorporated into the DMC charter.

For each PFS and each OS hypothesis, a Hwang-Shih-DeCani alpha-spending function with gamma parameter [redacted] is constructed to implement group sequential efficacy boundaries to control the type I error. The same spending function used for OS superiority hypotheses is also implemented to calculate boundaries for the non-inferiority hypotheses. Table 23 provides more details on the timing, number of events and decision guidance for each analysis. The actual boundaries and the alpha level will be determined from the overall alpha level after alpha-shifting as a result of a successful analysis and the actual number of events observed at the time of the interim analysis using the corresponding alpha-spending function.

In the event that superiority is declared for one or more PFS hypotheses at interim analysis 1, the study will continue to follow subjects for OS unless substantial treatment effect is demonstrated for all OS hypotheses at the significance level determined from the alpha-spending function as specified above.

Interim Analysis 1: interim PFS/OS analyses

The interim analysis will take place when all subjects have been followed up for at least 9 months.

Assuming 21 months enrollment period for 825 all subjects, interim analysis 1 is projected to occur 30 months after study start. The primary objective of the analyses is to demonstrate PFS superiority of pembrolizumab (monotherapy or in combination with chemotherapy).

At the time of interim analysis 1, the expected numbers of PFS events observed for the PFS hypotheses are specified below. If the actual number of events for a PFS hypothesis is different, the spending function boundaries will be adjusted accordingly for the actual number of events for that PFS hypothesis.

- ~211 PFS events between one experimental treatment and standard treatment in subjects with PD-L1 CPS 20 (H1 and H4)
- ~337 PFS events between one experimental treatment and standard treatment in subjects with PD-L1 CPS 1 (H2 and H5)
- ~423 PFS events between one experimental arm and standard treatment in all subjects (H3 and H6)

For the hypotheses of PFS superiority of one experimental treatment in subjects with PD-L1 CPS 20 (H1 and H4), alpha level of 0.19% is allocated to the test. The boundary to demonstrate PFS superiority of one experimental treatment over standard treatment corresponds to a one-sided p-value of [redacted], which corresponds to an approximate observed hazard ratio of [redacted] or less (approximately a [redacted] month or greater improvement over the median PFS from 6 months in the standard treatment arm).

If H1 is rejected, for the hypothesis of PFS superiority of pembrolizumab monotherapy in subjects with PD-L1 CPS 1 (H2), alpha level of 0.19% is shifted from H1. Similarly, if H4 is rejected, for the hypothesis of PFS superiority of pembrolizumab combination therapy in subjects with PD-L1 CPS 1 (H5), alpha level of 0.19% is shifted from H4. The boundary to demonstrate PFS superiority of one experimental treatment over standard treatment in subjects with PD-L1 CPS 1 corresponds to a one-sided p-value of 0.0012, which corresponds to an approximate observed hazard ratio of [redacted] or less (approximately a [redacted]-month or greater improvement over the median PFS from 6 months in the standard treatment arm).

If H1 and H2 are rejected, for the hypothesis of PFS superiority of pembrolizumab monotherapy in all subjects (H3), alpha level of 0.19% is shifted from H2. The boundary to demonstrate PFS superiority of pembrolizumab monotherapy over standard treatment in all subjects corresponds to a one-sided p-value of [redacted], which corresponds to an approximate

observed hazard ratio of [redacted] or less (approximately a [redacted]-month or greater improvement over the median PFS from 6 months in the standard treatment arm).

For the hypothesis of PFS superiority of pembrolizumab in combination with chemotherapy in all subjects (H6), alpha level of 0.02% is allocated to the test. The boundary to demonstrate PFS superiority of the experimental treatment over standard treatment corresponds to a one-sided p-value of [redacted], which corresponds to an approximate observed hazard ratio of [redacted] or less (approximately a [redacted]-month or greater improvement over the median PFS from 6 months in the standard treatment arm).

The trial will also examine OS at interim analysis 1. The expected numbers of events for the OS hypotheses are:

- ~171 deaths between one experimental arm and standard treatment in subjects with PD-L1 CPS 20 (H7 and H11)
- ~278 deaths between one experimental arm and standard treatment in subjects with PD-L1 CPS 1 (H8 and H12)
- ~352 deaths between one experimental arm and standard treatment in all subjects (H9, H10, H13 and H14)

The hazard ratio at bound, significance level and Z statistics of OS hypotheses provided in Table 23 are based on a nominal overall one-sided alpha level of 0.7% each to pembrolizumab monotherapy vs. standard treatment, and pembrolizumab in combination with chemotherapy vs. standard treatment, though the overall alpha levels for the OS hypotheses may be more than 0.7% due to alpha-shifting as a result of success in other hypotheses. The actual alpha level for an OS hypothesis will be recalculated if the overall alpha level is not the same as the specified nominal alpha level given the multiplicity strategy or the expected number of deaths is not observed.

Interim Analysis 2: interim OS analyses and final PFS analyses

The interim analysis will take place when all subjects have been followed up for at least 17 months.

Assuming 21 months enrollment period for 825 all subjects, interim analysis 2 is projected to occur 38 months after study start. The primary objective of the analyses is to demonstrate OS superiority of pembrolizumab (monotherapy or in combination with chemotherapy).

The expected numbers of events for the OS hypotheses are:

- ~205 deaths between one experimental arm and standard treatment in subjects with PD-L1 CPS 20 (H7, H11);
- ~332 deaths between one experimental arm and standard treatment in subjects with PD-L1 CPS 1 (H8, H12);
- ~421 deaths between one experimental arm and standard treatment in all subjects (H9, H10, H13 and H14).

However, if the expected number of events for an OS hypothesis is not observed, then the spending function boundaries will be adjusted accordingly for the smaller number of events for that OS hypothesis.

For the hypotheses of OS superiority of one experimental treatment in subjects with PD-L1 CPS 20 (H7 and H11), an alpha level of 0.7% is allocated to each test. The boundary to demonstrate OS superiority of one experimental treatment over standard treatment in PD-L1 CPS 20 corresponds to a one-sided p-value of [redacted], which corresponds to an approximate observed HR of [redacted] or less (approximately a [redacted]-month or greater improvement over the median OS from 10 months in the standard treatment arm).

If H7 is rejected, for the hypothesis of OS superiority of pembrolizumab monotherapy in subjects with PD-L1 CPS 1 (H8), an alpha level of 0.7% is shifted from H7. Similarly, if H11 is rejected, for the hypothesis of OS superiority of pembrolizumab combination therapy in subjects with PD-L1 CPS 1 (H12), alpha level of 0.7% is shifted from H11. The boundary to demonstrate OS superiority of one experimental treatment over standard treatment in PD-L1 CPS 1 corresponds to a one-sided p-value of [redacted], which corresponds to an approximate observed hazard ratio of [redacted] or less (approximately a [redacted]-month or greater improvement over the median OS from 10 months in the standard treatment arm).

If H7 through H9 are rejected, for the hypothesis of OS superiority of pembrolizumab monotherapy in all subjects (H10), alpha level of 0.7% is shifted from H9. The boundary to demonstrate OS superiority of pembrolizumab monotherapy over standard treatment in all subjects corresponds to a one-sided p-value of [redacted], which corresponds to an approximate observed hazard ratio of [redacted] or less (approximately a [redacted]-month or greater improvement over the median OS from 10 months in the standard treatment arm).

For the hypothesis of OS superiority of pembrolizumab in combination with chemotherapy in all subjects (H14), an alpha level of 0.7% is shifted to the test from H13. The boundary to demonstrate OS superiority of pembrolizumab in combination with chemotherapy over standard treatment in all subjects is same as the boundary for testing OS superiority of pembrolizumab monotherapy over standard treatment in all subjects

A second test of PFS, which is the final PFS analysis, will be conducted at interim analysis 2 only if superior PFS is not declared for that hypothesis at interim analysis 1. The expected numbers of PFS events at interim analysis 2 are:

- ~237 PFS events between one experimental treatment and standard treatment in subjects with PD-L1 CPS 20 (H1 and H4)
- ~378 PFS events between one experimental treatment and standard treatment in subjects with PD-L1 CPS 1 (H2 and H5)
- ~474 PFS events between one experimental treatment and standard treatment in all subjects (H3 and H6).

If the expected number of PFS events is not observed by the time the analysis is conducted, the remaining alpha as defined by the spending function will be accelerated to the analysis at that time, and the success boundary for PFS will be recalculated for the actual number of

events observed at that time considering the correlation between the interim and final PFS analyses data. Likewise, if the timing of events occurs faster than anticipated, the test boundary at the final PFS analysis will be adjusted to use the remaining Type I error not spent at earlier analysis.

Final Analysis: final OS analyses

The final analysis will take place when:

1) At least [redacted] deaths are observed between one experimental treatment and standard treatment in subjects with PD-L1 CPS 20 (H7 and H11);
2) At least [redacted] deaths are observed between one experimental treatment and standard treatment in subjects with PD-L1 CPS 1 (H8 and H12);
3) At least [redacted] deaths are observed between one experimental treatment and standard treatment in all subjects (H9, H10, H13 and H14);
4) All subjects have been followed up for at least 23 months.

The final analysis is expected to occur ~44 months after study start. For any hypothesis listed above, if superiority has not been declared at IA1 or IA2, the specified number of deaths is to be observed for the final analysis. If the expected number of deaths for a hypothesis is not observed by the time that the trial is open for 44 months, the timing of the final analysis may be delayed for up to 2 months or when the target death event numbers are observed, whichever occurs first. This calendar trigger will enable a suitable follow-up after IA2 and prevent the trial from continuing to an unreasonable duration. If at the time of the final analysis, the number of deaths for one hypothesis is not the same as specified above, the boundary at the final analysis will be adjusted to use the remaining Type I error not spent at earlier analyses.

Table 23 Decision Guidance at Each Analysis

Timing of Analysis	Testing	Expected number of events	Value at boundary	Efficacy Boundary†
IA1 (interim PFS analyses and interim OS analyses)				
30 mos from study start; all 825 subjects enrolled and followed up for at least 9 months	PFS mono/combo vs. SOC in subjects with PD-L1 CPS 20 (H1/H4)	~211	Z statistic p-value (one-sided) Approx. observed HR	[redacted]
	PFS mono/combo vs. SOC in subjects with PD-L1 CPS 1 (H2/H5)	~337	Z statistic p-value (one-sided) Approx. observed HR	
	PFS mono vs. SOC in all subjects (H3)	~423	Z statistic p-value (one-sided) Approx. observed HR	
	PFS combo vs. SOC in all subjects (H6)	~423	Z statistic p-value (one-sided) Approx. observed HR	
	OS mono/combo vs. SOC in subjects with PD-L1 CPS 20 (H7/H11)	~171	Z statistic p-value (one-sided) Approx. observed HR	
	OS mono/combo vs. SOC in subjects with PD-L1 CPS 1 (H8/H12)	~278	Z statistic p-value (one-sided) Approx. observed HR	
	OS non-inferiority mono/combo vs. SOC in all subjects (H9/H13)*	~352	Z statistic p-value (one-sided) Approx. observed HR	
	OS superiority mono/combo vs. SOC in all subjects (H10/H14)	~352	Z statistic p-value (one-sided) Approx. observed HR	

Timing of Analysis	Testing	Expected number of events	Value at boundary	Efficacy Boundary†
IA2 (interim OS analyses and final PFS analyses)				
38 mos from study start; all 825 subjects enrolled and followed up for at least 17 months	PFS mono/combo vs. SOC in subjects with PD-L1 CPS 20 (H1/H4)	~237	Z statistic p-value (one-sided) Approx. observed HR	[redacted]
	PFS mono/combo vs. SOC in subjects with PD-L1 CPS 1 (H2/H5)	~378	Z statistic p-value (one-sided) Approx. observed HR	
	PFS mono vs. SOC in all subjects (H3)	~474	Z statistic p-value (one-sided) Approx. observed HR	
	PFS combo vs. SOC in all subjects (H6)	~474	Z statistic p-value (one-sided) Approx. observed HR	
	OS mono/combo vs. SOC in subjects with PD-L1 CPS 20 (H7/H11)	~205	Z statistic p-value (one-sided) Approx. observed HR	
	OS mono/combo vs. SOC in subjects with PD-L1 CPS 1 (H8/H12)	~332	Z statistic p-value (one-sided) Approx. observed HR	
	OS non-inferiority mono/combo vs. SOC in all subjects (H9/H13)*	~421	Z statistic p-value (one-sided) Approx. observed HR	
	OS superiority mono/combo vs. SOC in all subjects (H10/H14)	~421	Z statistic p-value (one-sided) Approx. observed HR	

Timing of Analysis	Testing	Expected number of events	Value at boundary	Efficacy Boundary†
Final Analysis (Final OS Analysis)				
[redacted] from study start	OS mono/combo vs. SOC in subjects with PD-L1 CPS 20 (H7/H11)	≥222	Z statistic p-value (one-sided) Approx. observed HR	[redacted]
	OS mono/combo vs. SOC in subjects with PD-L1 CPS 1 (H8/H12)	≥359	Z statistic p-value (one-sided) Approx. observed HR	
	OS non-inferiority mono/combo vs. SOC in all subjects (H9/H13)*	≥455	Z statistic p-value (one-sided) Approx. observed HR	
	OS superiority mono/combo vs. SOC in all subjects (H10/H14)	≥455	Z statistic p-value (one-sided) Approx. observed HR	

† Efficacy decision rules for OS presented in table do not account for any alpha-shifting from other hypotheses as a result of a successful analysis. P-values based on spending functions determine significance of tests; hazard ratios corresponding to significance are approximate.
*NI bounds are calculated with HR=0.85 under the alternative to establish non-inferiority (NI margin=1.2).

For the PFS analysis, in the scenario that events have accumulated faster than expected, event-based analysis will not allow for observing tail behavior that has been important in other trials to fully describe the treatment effect over time. For PFS hypotheses, the Lan and DeMets (1989) [62] calendar time method will be used for alpha-spending to generate the group sequential design. The timing and alpha level of the original plan will be maintained for PFS hypotheses, regardless of the number of events observed. The sample space ordering required for group-sequential trials as justified by Maurer and Bretz (2013) [57] will be maintained. This ensures strong control of Type I error. The updated bounds for the PFS hypotheses are given in Table 24. The bounds are based on initial alpha allocation. A Hwang-Shih-DeCani [63] (-1.073) spending function has been used to implement alpha spending for PFS hypotheses for monotherapy versus SOC in all populations (H1, H2, and H3) and combination therapy versus control with PD-L1 CPS1 and CPS20 (H4 and H5). A Hwang-Shih-DeCani (-3.079) spending function has been used for the PFS hypothesis for combination therapy versus control in all subjects (H6). The actual boundaries and the alpha level will be determined from the overall alpha level after any alpha shifting as a result of a successful analysis. The alpha level at the final analysis for the PFS hypotheses (IA2) will be calculated based on alpha reallocation, the alpha used at the interim analysis, and the actual number of events at IA1 and the final PFS analysis (IA2). The bounds given in Table 24 will be adjusted accordingly.

Table 24 Decision Guidance for PFS hypotheses at Each Analysis

Timing of Analysis	Testing	Expected number of events	Value at boundary	Efficacy Boundary[†]
IA1 (interim PFS analyses)				
30 mos from study start; all 825 subjects enrolled and followed up for at least 9 months	PFS mono/combo vs. SOC in subjects with PD-L1 CPS 20 (H1/H4)	~211	Z statistic	3.0357
			p-value (one-sided)	0.0012
			Approx. observed HR	0.6581
	PFS mono/combo vs. SOC in subjects with PD-L1 CPS 1 (H2/H5)	~337	Z statistic	3.0357
			p-value (one-sided)	0.0012
			Approx. observed HR	0.7184
	PFS mono vs. SOC in all subjects (H3)	~423	Z statistic	3.0357
			p-value (one-sided)	0.0012
			Approx. observed HR	0.7441
	PFS combo vs. SOC in all subjects (H6)	~423	Z statistic	3.7190
			p-value (one-sided)	0.0001
			Approx. observed HR	0.6965
IA2 (final PFS analyses)				
38 mos from study start; all 825 subjects enrolled and followed up for at least 17 months	PFS mono/combo vs. SOC in subjects with PD-L1 CPS 20 (H1/H4)	~237	Z statistic	2.9775
			p-value (one-sided)	0.0015
			Approx. observed HR	0.6792
	PFS mono/combo vs. SOC in subjects with PD-L1 CPS 1 (H2/H5)	~378	Z statistic	2.9755
			p-value (one-sided)	0.0015
			Approx. observed HR	0.7363
	PFS mono vs. SOC in all subjects (H3)	~474	Z statistic	2.9755
			p-value (one-sided)	0.0015
			Approx. observed HR	0.7606
	PFS combo vs. SOC in all subjects (H6)	~474	Z statistic	3.5924
			p-value (one-sided)	0.0002
			Approx. observed HR	0.7188

[†] Efficacy decision rules for PFS presented in table do not account for any alpha shifting from other hypotheses as a result of a successful analysis. P-values based on spending functions determine significance of tests; hazard ratios corresponding to significance are approximate.

8.2.10 Compliance (Medication Adherence)

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

8.2.11 Extent of Exposure

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

9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.1 Investigational Product

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

Table 25 Product Descriptions

Product Name & Potency	Dosage Form	Comments
Pembrolizumab (MK-3475) 100 mg/4 mL	Solution for infusion	Provided centrally by the Sponsor
Cetuximab 100 mg/20 mL	Solution for infusion	Provided centrally by the Sponsor or locally by the trial site, subsidiary or designee
Carboplatin 600 mg/60 mL	Solution for infusion	Provided centrally by the Sponsor or locally by the trial site, subsidiary or designee
Cisplatin 50 mg/50 mL	Solution for infusion	Provided centrally by the Sponsor or locally by the trial site, subsidiary or designee
Fluorouracil 1000 mg/20 mL; Fluorouracil 500 mg/10 mL	Solution for infusion	Provided centrally by the Sponsor or locally by the trial site, subsidiary or designee

9.2 Packaging and Labeling Information

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

9.3 Clinical Supplies Disclosure

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

9.4 Storage and Handling Requirements

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

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

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

9.5 Returns and Reconciliation

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

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

9.6 Standard Policies

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

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

10.1 Confidentiality

10.1.1 Confidentiality of Data

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

10.1.2 Confidentiality of Subject Records

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

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

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

10.1.3 Confidentiality of Investigator Information

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

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

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

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

10.1.4 Confidentiality of IRB/IEC Information

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

10.2 Compliance with Financial Disclosure Requirements

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

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

10.3 Compliance with Law, Audit and Debarment

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

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

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

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

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

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

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

11.0 LIST OF REFERENCES

1. Disis ML. Immune regulation of cancer. J Clin Oncol 2010; 28(29):4531-8.

2. Dong H, Strome SE, Salomao DR, Tamura H, Hirano F, Flies DB, et al. Tumor-associated B7-H1 promotes T-cell apoptosis: a potential mechanism of immune evasion. Nat Med 2002;8(8):793-800.

3. Sharpe AH, Freeman GJ. The B7-CD28 superfamily. Nature 2002;2:116-26.

4. Brown JA, Dorfman DM, Ma F-R, Sullivan EL, Munoz O, Wood CR, et al. Blockade of programmed death-1 ligands on dendritic cells enhances T cell activation and cytokine production. J Immunol 2003;170:1257-66.

5. Francisco LM, Sage PT, Sharpe AH. The PD-1 pathway in tolerance and autoimmunity. Immunol Rev 2010;236:219-42.

6. Thompson RH, Dong H, Lohse CM, Leibovich BC, Blute ML, Cheville JC, et al. PD-1 expressed by tumor-infiltrating immune cells and is associated with poor outcome for patients with renal cell carcinoma. Clin Caner Res 2007;13(6):1757-61.

7. Talmadge JE, Donkor M, Scholar E. Inflammatory cell infiltration of tumors: Jekyll or Hyde. Cancer Metastasis Rev 2007;26:373-400.

8. Usubütün A, Ayhan A, Uygur MC, Ozen H, Toklu C, Ruacan S. Prognostic factors in renal cell carcinoma. J Exp Clin Cancer Res 1998;17(1):77-81.

9. Al-Shibli KI, Donnem T, Al-Saad S, Persson M, Bremnes RM, Busund L-T. Prognostic effect of epithelial and stromal symphocyte infiltration in non-small cell lung cancer. Clin Cancer Res 2008;14(16):5220-7.

10. Deschoolmeester V, Baay M, Van Marck E, Weyler J, Vermeulen p, Lardon F, et al. Tumor infiltrating lymphocytes: an intriguing player in the survival of colorectal cancer patients. BMC Immunol 2010;11:19.

11. Diez M, Pollán M, Enriquez JM, Dominguez P, Santana A, Tobaruela E, et al. Histopathologic prognostic score in colorectal adenocarcinomas. Anticancer Res 1998;18:689-94.

12. Galon J, Costes A, Sanchez-Cabo F, Kirilovsky A, Mlecnik B, Lagorce-Pagès C, et al. Type, density, and location of immune cells within human colorectal tumors predict clinical outcome. Science 2006;313:1960-4.

13. Hiraoka N. Tumor-infiltrating lymphocytes and hepatocellular carcinoma: molecular biology. Int J Clin Oncol 2010;15:544-51.

14. Nobili C, Degrate L, Caprotti R, Franciosi C, Leone BE, Trezzi R, et al. Prolonged survival of a patient affected by pancreatic adenocarcinoma with massive lymphocyte and dendritic cell infiltration after interleukin-2 immunotherapy. Report of a case. Tumori 2008;94:426-30.

15. Hodi FS, Dranoff G. The biologic importance of tumor-infiltrating lymphocytes. J Cutan Pathol 2010;37(Suppl 1):48-53.

16. Kloor M. Lymphocyte infiltration and prognosis in colorectal cancer. Lancet 2009;10:840-841.

17. Hillen F, Baeten CIM, van de Winkel A, Creytens D, van der Schaft DWJ, Winnepenninckx V, et al. Leukocyte infiltration and tumor cell plasticity are parameters of aggressiveness in primary cutaneous melanoma. Cancer Immunol Immunother 2008;57:97-106.

18. Lee HE, Chae SW, Lee YJ, Kim MA, Lee HS, Lee BL, et al. Prognostic implications of type and density of tumour-infiltrating lymphocytes in gastric cancer. Br J Cancer 2008;99(10):1704-11.

19. Leffers N, Gooden MJM, de Jong RA, Hoogeboom B-N, ten Hoor KA, Hollema H, et al. Prognostic significance of tumor-infiltrating T-lymphocytes in primary and metastatic lesions of advanced stage ovarian cancer. Cancer Immunol Immunother 2009;58:449-59.

20. Nishimura H, Honjo T, Minato N. Facilitation of β selection and modification of positive selection in the thymus of PD-1-deficient mice. J Exp Med 2000;191(5):891-7.

21. Liotta F, Gacci M, Frosali F, Querci V, Vittori G, Lapini A, et al. Frequency of regulatory T cells in peripheral blood and in tumour-infiltrating lymphocytes correlates with poor prognosis in renal cell carcinoma. BJU Intern 2010;107:1500-6.

22. Ropponen KM, Eskelinen MJ, Lipponen PK, Alhava E, Kosma V-M. Prognostic value of tumour-infiltrating lymphocytes (TILs) in colorectal cancer. J Pathol 1997;182:318-24.

23. Dudley ME, Wunderlich JR, Yang JC, Sherry RM, Topalian SL, Restifo NP, et al. Adoptive cell transfer therapy following non-myeloablative but lymphodepleting chemotherapy for the treatment of patients with refractory metastatic melanoma. J Clin Oncol 2005;23(10):2346-57.

24. Hunder NN, Wallen H, Cao J, Hendricks DW, Reilly JZ, Rodmyre R, et al. Treatment of metastatic melanoma with autologous CD4+ T cells against NY-ESO-1. N Engl J Med 2008;358(25):2698-703.

25. Pölcher M, Braun M, Friedrichs N, Rudlowski C, Bercht E, Fimmers R, et al. Foxp3+ cell infiltration and granzyme B+/Foxp3+ cell ratio are associated with outcome in neoadjuvant chemotherapy-treated ovarian carcinoma. Cancer Immunol Immunother 2010;59:909-19.

26. Okazaki T, Maeda A, Nishimura H, Kurosaki T, Honjo T. PD-1 immunoreceptor inhibits B cell receptor-mediated signaling by recruiting src homology 2-domain-containing tyrosine phosphatase 2 to phosphotyrosine. PNAS 2001;98(24):13866-71.

27. Greenwald RJ, Freeman GJ, Sharpe AH. The B7 family revisted. Annu Rev Immunol 2005;23:515-48.

28. Chow L, Mehra R, Haddad R, Gupta S, Weiss J, Berger R, Burtness B, Tahara M, Keam B, Le D, Cheng J, Heath K, Pathiraja K, Seiwert T. A phase Ib study of MK-3475 in patients with human papillomavirus (HPV) associated and non-HPV associated head and neck (H/N) cancer. ESMO 2015 Abstract #2866, Sep 2015.

29. Mehra R, Seiwert T, Mahipal A, Weiss J, Berger R, Eder J, Burtness B, Tahara M, Keam B, Le D, Muro K, Geva R, Chung H, Lin C, Meister A, Hille D, Cheng D, Chow L, Haddad R. Efficacy and safety of pembrolizumab in recurrent/metastatic head and neck squamous cell carcinoma (R/M HNSCC): Pooled analyses after long-term follow-up in KEYNOTE-012. ASCO 2016 Abstract #6012, Jun 2016.

30. Price K, Cohen E. Current treatment options for metastatic head and neck cancer. Curr Treat Options Oncol. 2012 Mar; 13(1):35-46.

31. Bauml J, Seiwert T, Pfister D, Worden F, Liu S, Gilbert J, Saba N, Weiss J, Wirth L, Sukari A, Kang H, Gibson M, Massarelli E, Powell S, Meister A, Shu X, Cheng J, Haddad R. Preliminary results from KEYNOTE-055: Pembrolizumab after platinum and cetuximab failure in head and neck squamous cell carcinoma (HNSCC). ASCO 2016 Abstract #6011, Jun 2016.

32. Chow L, Mehra R, Haddad R, Mahipal A, Weiss J, Berger R, Eder J, Burtness B, Tahara M, Keam B, Le D, Muro K, Geva R, Chung H, Lin C, Ayers M, Aurora-Garg D, Lunceford J, Cheng J, Seiwert T. Biomarkers and response to pembrolizumab (pembro) in recurrent/metastatic head and neck squamous cell carcinoma (R/M HNSCC). ASCO 2016 Abstract #6010, Jun 2016.

33. Liverpool consortium (1990). "A phase III randomised trial of cisplatin, methotrextate, cisplatin + methotrexate and cisplatin + 5-FU in end stage squamous carcinoma of the head and neck. Liverpool Head and Neck Oncology Group." Br J Cancer 61(2): 311-315.

34. Forastiere, A. A., T. Leong, E. Rowinsky, B. A. Murphy, D. R. Vlock, R. C. DeConti and G. L. Adams (2001). "Phase III comparison of high-dose paclitaxel + cisplatin + granulocyte colony-stimulating factor versus low-dose paclitaxel + cisplatin in advanced head and neck cancer: Eastern Cooperative Oncology Group Study E1393." J Clin Oncol 19(4): 1088-1095.

35. Forastiere, A. A., B. Metch, D. E. Schuller, J. F. Ensley, L. F. Hutchins, P. Triozzi, J. A. Kish, S. McClure, E. VonFeldt, S. K. Williamson and et al. (1992). "Randomized comparison of cisplatin plus fluorouracil and carboplatin plus fluorouracil versus methotrexate in advanced squamous-cell carcinoma of the head and neck: a Southwest Oncology Group study." J Clin Oncol 10(8): 1245-1251.

36. Gibson, M. K., Y. Li, B. Murphy, M. H. Hussain, R. C. DeConti, J. Ensley, A. A. Forastiere and G. Eastern Cooperative Oncology (2005). "Randomized phase III evaluation of cisplatin plus fluorouracil versus cisplatin plus paclitaxel in advanced head and neck cancer (E1395): an intergroup trial of the Eastern Cooperative Oncology Group." J Clin Oncol 23(15): 3562-3567.

37. Jacobs C1, L. G., Velez-García E, Sridhar KS, Knight W, Hochster H, Goodnough LT, Mortimer JE, Einhorn LH, Schacter L, et al. (1992). "A phase III randomized study comparing cisplatin and fluorouracil as single agents and in combination for advanced squamous cell carcinoma of the head and neck." J Clin Oncol 10(2): 257-263.

38. Schornagel, J. H., J. Verweij, P. H. de Mulder, F. Cognetti, J. B. Vermorken, P. Cappelaere, J. P. Armand, J. Wildiers, A. de Graeff, M. Clavel and et al. (1995). "Randomized phase III trial of edatrexate versus methotrexate in patients with metastatic and/or recurrent squamous cell carcinoma of the head and neck: a European Organization for Research and Treatment of Cancer Head and Neck Cancer Cooperative Group study." J Clin Oncol 13(7): 1649-1655.

39. Schrijvers, D., J. Johnson, U. Jiminez, M. Gore, P. Kosmidis, H. Szpirglas, K. Robbins, J. Oliveira, R. Lewensohn, J. Schuller, A. Riviere, C. Arvay, P. Langecker, H. Jacob, E. Cvitkovic and E. Vokes (1998). "Phase III trial of modulation of cisplatin/fluorouracil chemotherapy by interferon alfa-2b in patients with recurrent or metastatic head and neck cancer. Head and Neck Interferon Cooperative Study Group." J Clin Oncol 16(3): 1054-1059.

40. Vermorken, J. B., R. Mesia, F. Rivera, E. Remenar, A. Kawecki, S. Rottey, J. Erfan, D. Zabolotnyy, H. R. Kienzer, D. Cupissol, F. Peyrade, M. Benasso, I. Vynnychenko, D. De Raucourt, C. Bokemeyer, A. Schueler, N. Amellal and R. Hitt (2008). "Platinum-based chemotherapy plus cetuximab in head and neck cancer." N Engl J Med 359(11): 1116-1127.

41. Parker, D., Bray, F., Ferlay, J., Pisani, P. Global Cancer Statistics, 2002. CA Cancer J Clin. 2005;55(2):74-108

42. Peyrade, F., D. Cupissol, L. Geoffrois, F. Rolland, C. Borel, C. Ciais, S. Faivre and J. Guigay (2013). "Systemic treatment and medical management of metastatic squamous cell carcinoma of the head and neck: review of the literature and proposal for management changes." Oral Oncol 49(6): 482-491.

43. Fakhry C, Westra WH, Li S, Cmelak A, Ridge JA, Pinto H, et al. Improved survival of patients with human papillomavirus-positive head and neck squamous cell carcinoma in a prospective clinical trial. J Natl Cancer Inst 2008;100:261-9.

44. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 1993;85(5):365-76.

45. Mehanna HM and Morton RP. Patient's views on the utility of quality of life questionnaires in head and neck cancer: a randomized trial. Clin. Otolaryngol. 2006;31:310-316.

46. Tschiesner U, Rogers SN, Harreus U, Berghaus A, Cieza A. Content comparison of quality of life questionnaires used in head and neck cancer based on the international classification of functioning, disability and health: a systemic review. Eur Arch Otorhinolaryngol. 2008;265:627-637.

47. Bjordal K, Ahlner-Elmquist MA, Tollesson E, Jensen AB, Razavi D, Maher EJ, et al. Development of a European Organization for Research and Treatment of Cancer (EORTC) questionnaire module to be used in quality of life assessments in head and neck cancer patients. Acta Oncologica. 1994;33(8):879-885.

48. Bjordal K, de Graeff A, Fayers PM, Hammerlid E, van Pottelsberghe C, Curran D, et al. A 12 country field study of the EORTC QLQ-C30 (version 3.0) and the head and neck cancer specific module (EORTC QLQ-H&N35) in head and neck patients. EORTC Quality of Life Group. Eur J Cancer. 2000 Sep;36(14):1796-807.

49. Chera BS, Eisbruch A, Murphy BA, Ridge JA, Gavin P, Reeve BB, et al. Recommended patient-reported core set of symptoms to measure in head and neck cancer treatment trials. J Natl Cancer Inst. 2014 Jul 8;106(7):[4 p.].

50. Mesia R, Rivera F, Kawecki A, Rottey S, Hitt R, Kienzer H, et al. Quality of life of patients receiving platinum-based chemotherapy plus cetuximab first line for recurrent and/or metastatic squamous cell carcinoma of the head and neck. Ann Oncol. 2010 Oct;21(10):1967-73.

51. Machiels J, Haddad RI, Fayette J, Licitra LF, Tahara M, Vermorken JB et al. Afatinib versus methotrexate as second-line treatment for patients with R/M HNSCC who progressed after platinum-based therapy: primary efficacy results of LUX-head and neck 1, a phase III trial. ESMO 2014 Congress; 2014 Sep 27; Madrid, ES. 2014.

52. Osoba D, Rodrigues G, Myles J, Zee B, Pater J. Interpreting the significance of changes in health-related quality-of-life scores. J Clin Oncol 1998;16:139-44.

53. King MT. The interpretation of scores from the EORTC quality of life questionnaire QLQ-C30. Quality of Life Research 1996;5:555-67.

54. Rivera F, Garcia-Castaño A, Vega N, Vega-Villegas ME, & Guitiérrez-Sanz L. Cetuximab in metastatic or recurrent head and neck cancer: the EXTREME trial. Expert Rev Anticancer Ther. 2009;9(10):1421-1428.

55. Robins JM, Tsiatis AA. Correcting for non-compliance in randomized trials using rank preserving structural failure time models. Communication in Statistics – Theory and Methods 1991;20(8):2609-2631.

56. Miettinen O, Nurminen M. Comparative Analysis of two rates. Statistics in Medicine 1985;4:213-226.

57. Maurer W, Bretz F. Multiple Testing in Group Sequential Trials Using Graphical Approaches. Statistics in Biopharmaceutical Research 2013;5(4):311-320

58. Bossi P, Miceli R, Locati LD, Ferrari D, Vecchio S, Moretti G, et al. A randomized, phase 2 study of cetuximab plus cisplatin with or without paclitaxel for the first-line treatment of patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck. Ann Oncol. 2017 Sep 8. [Epub ahead of print].

59. Vermorken JB, Peyrade F, Krauss J, Mesía R, Remenar E, Gauler TC, et al. Cisplatin, 5-fluorouracil, and cetuximab (PFE) with or without cilengitide in recurrent/metastatic squamous cell carcinoma of the head and neck: results of the randomized phase I/II ADVANTAGE trial (phase II part). Annals of Oncology. 2014;25(3):682–8.

60. Cohen EEW, Saba NF, Gitlitz B, Haddad R, Sukari A, Neupane P, et al. Active8: A randomized, double-blind, placebo-controlled phase 2 study of chemotherapy plus cetuximab in combination with motolimod immunotherapy in patients with recurrent or metastatic squamous cell carcinoma of the head and neck. Poster session presented at European Society for Medical Oncology, 2016 Oct 7-11; Copenhagen, DK.

61. Cohen EE, Harrington KJ, Le Tourneau C, Dinis J, Licitra L, Ahn MJ, et al. Head and neck cancer, excluding thyroid - Pembrolizumab (pembro) vs standard of care (SOC) for recurrent or metastatic head and neck squamous cell carcinoma (R/M HNSCC): Phase 3 KEYNOTE-040 trial. [abstract]. ESMO. 2017;28:5. Abstract no. 628.

62. Lan KKG, DeMets DL. Group sequential procedures: calendar versus information time. Stat Med. 1989;8:1191-8.

63. Hwang IK, Shih WJ, De Cani JS. Group sequential designs using a family of type I error probability spending functions. Stat Med. 1990;9:1439-45.

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 leftover 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 leftover 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.

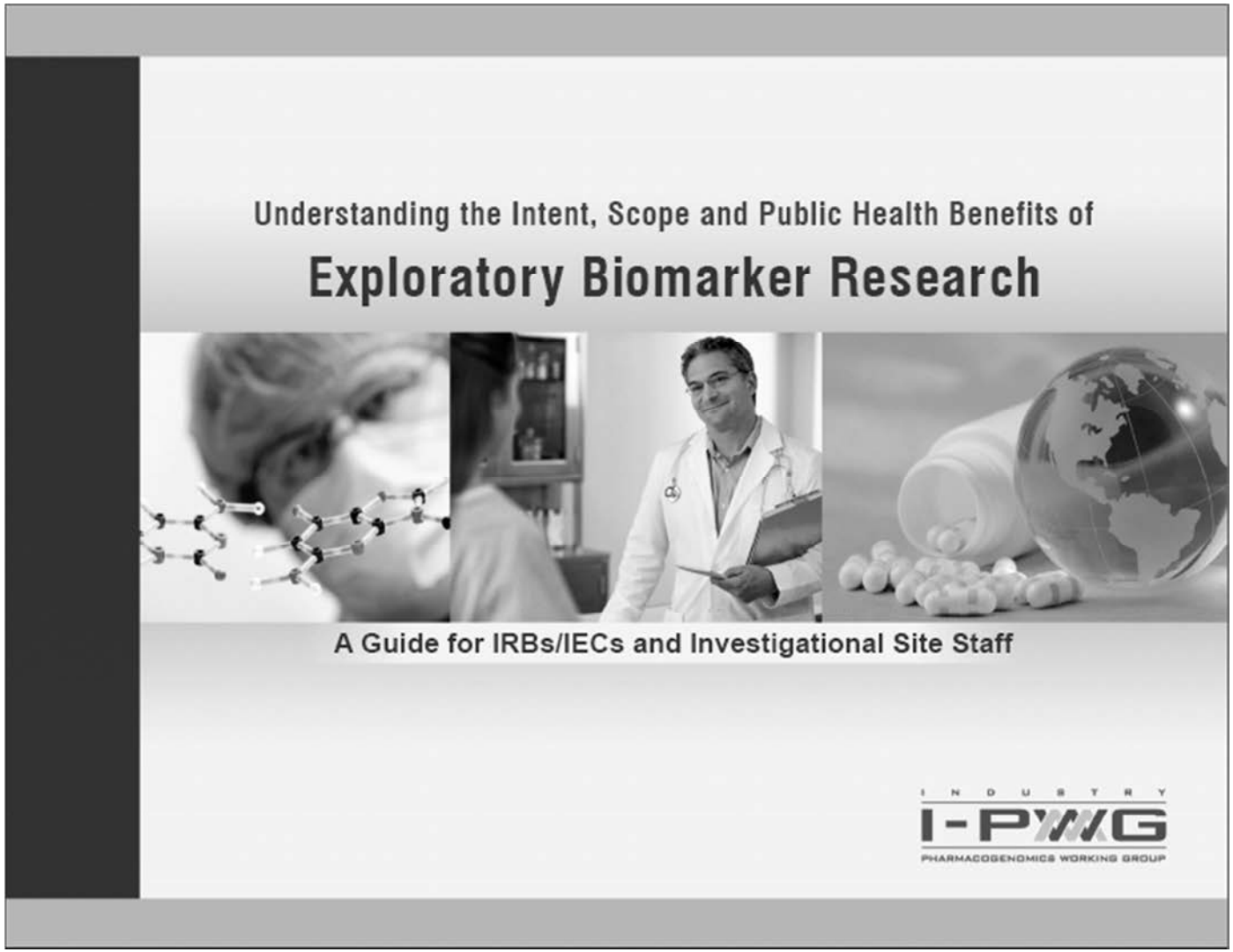
13. Questions

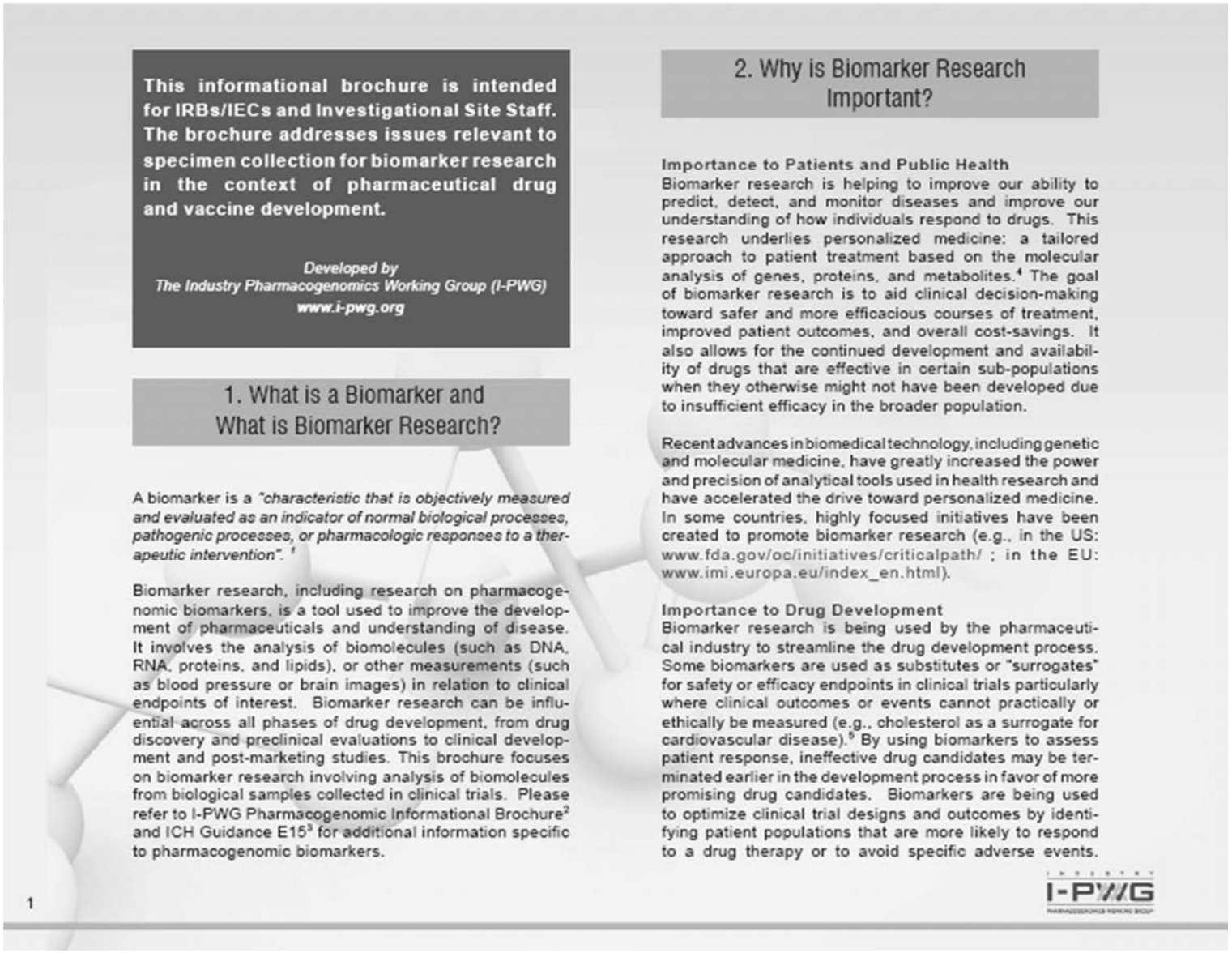
Any questions related to the future biomedical research should be e-mailed directly to clinical.specimen.management@merck.com.

14. 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?

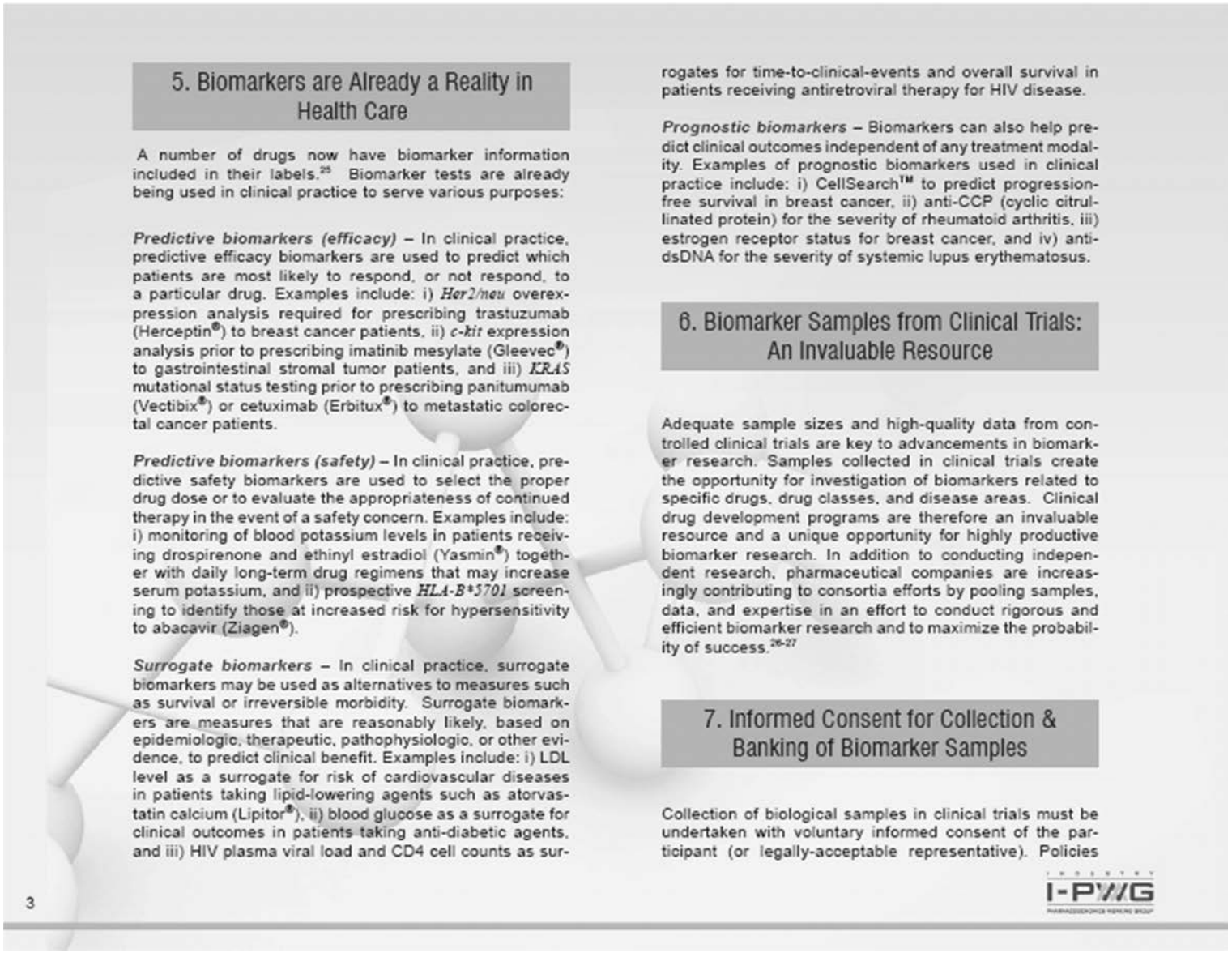
Biomarker research is currently being used in drug/vaccine development to:

- 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.

2

I-PWG



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

3

I-PWG

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]

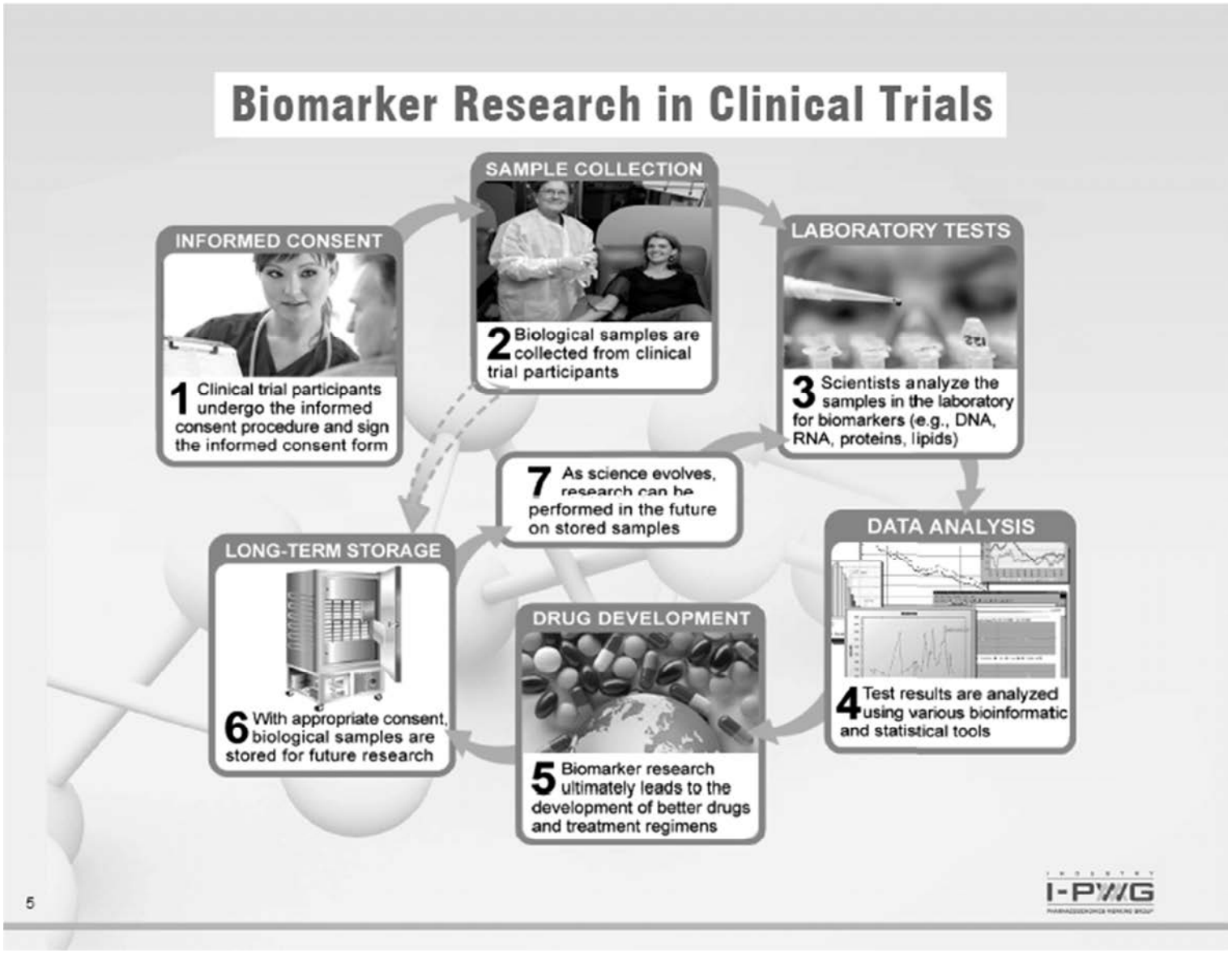
The scope of research – Where the scope of the potential future research is broad, participants should be informed of the boundaries of the research. While it may not be possible to describe the exact analytical techniques that will be used, or specific molecules that will be analyzed, it is possible 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.

4

I-PWG


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
5
I-PWG

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

6

I-PWG

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]

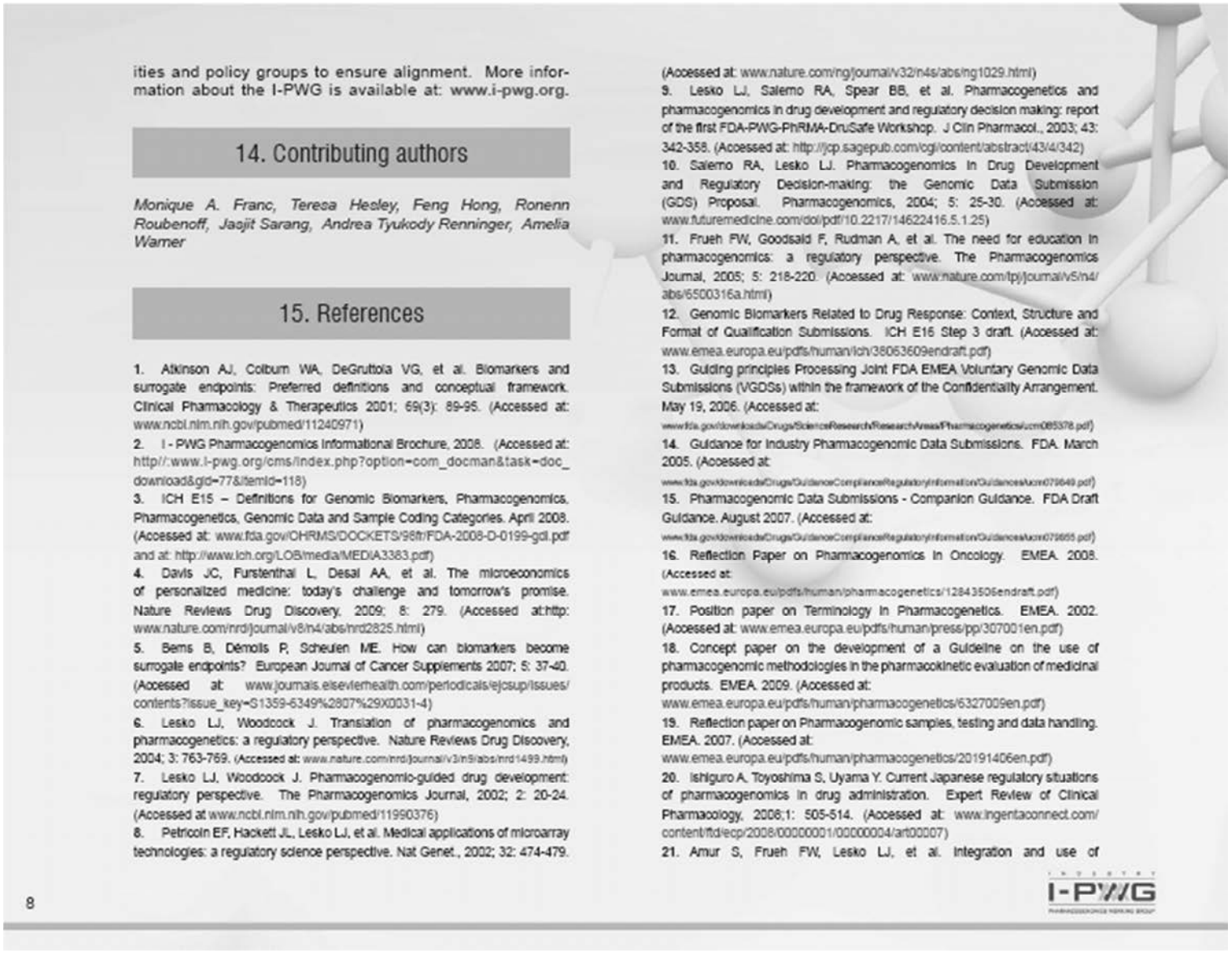
12.Where to Get More Information?

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-

7



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

14. Contributing authors

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

15. References

1. Atkinson AJ, Colburn WA, DeGruttola VG, et al. Biomarkers and surrogate endpoints: Preferred definitions and conceptual framework. Clinical Pharmacology & Therapeutics 2001; 69(3): 89-95. (Accessed at: www.ncbi.nlm.nih.gov/pubmed/11240971)
2. I - PWG Pharmacogenomics Informational Brochure, 2008. (Accessed at: http//:www.i-pwg.org/cms/index.php?option=com_docman&task=doc_download&gid=77&Itemid=118)
3. ICH E15 – Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories. April 2008. (Accessed at: www.fda.gov/OHRMS/DOCKETS/98fr/FDA-2008-D-0199-gdl.pdf and at: http://www.ich.org/LOB/media/MEDIA3383.pdf)
4. Davis JC, Furstenthal L, Desai AA, et al. The microeconomics of personalized medicine: today's challenge and tomorrow's promise. Nature Reviews Drug Discovery, 2009; 8: 279. (Accessed at:http: www.nature.com/nrd/journal/v8/n4/abs/nrd2825.html)
5. Bems B, Démolis P, Scheulen ME. How can biomarkers become surrogate endpoints? European Journal of Cancer Supplements 2007; 5: 37-40. (Accessed at: www.journals.elsevierhealth.com/periodicals/ejcsup/issues/contents?issue_key=S1359-6349%2807%29X0031-4)
6. Lesko LJ, Woodcock J. Translation of pharmacogenomics and pharmacogenetics: a regulatory perspective. Nature Reviews Drug Discovery, 2004; 3: 763-769. (Accessed at: www.nature.com/nrd/journal/v3/n9/abs/nrd1499.html)
7. Lesko LJ, Woodcock J. Pharmacogenomic-guided drug development: regulatory perspective. The Pharmacogenomics Journal, 2002; 2: 20-24. (Accessed at www.ncbi.nlm.nih.gov/pubmed/11990376)
8. Petricoin EF, Hackett JL, Lesko LJ, et al. Medical applications of microarray technologies: a regulatory science perspective. Nat Genet., 2002; 32: 474-479. (Accessed at: www.nature.com/ng/journal/v32/n4s/abs/ng1029.html)
9. Lesko LJ, Salerno RA, Spear BB, et al. Pharmacogenetics and pharmacogenomics in drug development and regulatory decision making: report of the first FDA-PWG-PhRMA-DruSafe Workshop. J Clin Pharmacol., 2003; 43: 342-358. (Accessed at: http://jcp.sagepub.com/cgi/content/abstract/43/4/342)
10. Salerno RA, Lesko LJ. Pharmacogenomics in Drug Development and Regulatory Decision-making: the Genomic Data Submission (GDS) Proposal. Pharmacogenomics, 2004; 5: 25-30. (Accessed at: www.futuremedicine.com/doi/pdf/10.2217/14622416.5.1.25)
11. Frueh FW, Goodsaid F, Rudman A, et al. The need for education in pharmacogenomics: a regulatory perspective. The Pharmacogenomics Journal, 2005; 5: 218-220. (Accessed at: www.nature.com/tpj/journal/v5/n4/abs/6500316a.html)
12. Genomic Biomarkers Related to Drug Response: Context, Structure and Format of Qualification Submissions. ICH E16 Step 3 draft. (Accessed at: www.emea.europa.eu/pdfs/human/ich/38063609endraft.pdf)
13. Guiding principles Processing Joint FDA EMEA Voluntary Genomic Data Submissions (VGDSs) within the framework of the Confidentiality Arrangement. May 19, 2006. (Accessed at: www.fda.gov/downloads/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm085378.pdf)
14. Guidance for Industry Pharmacogenomic Data Submissions. FDA. March 2005. (Accessed at: www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079849.pdf)
15. Pharmacogenomic Data Submissions - Companion Guidance. FDA Draft Guidance. August 2007. (Accessed at: www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079855.pdf)
16. Reflection Paper on Pharmacogenomics in Oncology. EMEA. 2008. (Accessed at: www.emea.europa.eu/pdfs/human/pharmacogenetics/12843506endraft.pdf)
17. Position paper on Terminology in Pharmacogenetics. EMEA. 2002. (Accessed at: www.emea.europa.eu/pdfs/human/press/pp/307001en.pdf)
18. Concept paper on the development of a Guideline on the use of pharmacogenomic methodologies in the pharmacokinetic evaluation of medicinal products. EMEA. 2009. (Accessed at: www.emea.europa.eu/pdfs/human/pharmacogenetics/6327009en.pdf)
19. Reflection paper on Pharmacogenomic samples, testing and data handling. EMEA. 2007. (Accessed at: www.emea.europa.eu/pdfs/human/pharmacogenetics/20191406en.pdf)
20. Ishiguro A, Toyoshima S, Uyama Y. Current Japanese regulatory situations of pharmacogenomics in drug administration. Expert Review of Clinical Pharmacology, 2008;1: 505-514. (Accessed at: www.ingentaconnect.com/content/ftd/ecp/2008/00000001/00000004/art00007)
21. Amur S, Frueh FW, Lesko LJ, et al. Integration and use of

8

I-PWG

biomarkers in drug development, regulation and clinical practice: A US regulatory practice. Biomarkers Med. 2008; 2, 305-311. (Accessed at: www.ingentaconnect.com/content/fm/bmm/2008/00000002/00000003/art00010?crawler=true)

22. Mendrick DL, Brazell C, Mansfield EA, et al. Pharmacogenomics and regulatory decision making: an international perspective. The Pharmacogenomics Journal. 2006; 6(3), 154-157. (Accessed at: www.nature.com/tpj/journal/v6/n3/abs/6500364a.html)

23. Pendergast MK. Regulatory agency consideration of pharmacogenomics. Exp Biol Med (Maywood). 2008; 233:1498-503. (Accessed at: www.ebmonline.org/cgi/content/abstract/233/12/1498)

24. Goodsaid F, Frueh F. Process map proposal for the validation of genomic biomarkers. Pharmacogenomics., 2006; 7(5):773-82 (Accessed at: www.futuremedicine.com/doi/abs/10.2217/14622416.7.5.773)

25. FDA Table of Valid Genomic Biomarkers in the Context of Approved Drug Labels. (Accessed at: www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm)

26. International Serious Adverse Event Consortium. (Accessed at: www.saeconsortium.org)

27. Predictive Safety Testing Consortium. (Accessed at: www.c-path.org/pstc.cfm)

28. Nuremberg code. (Accessed at: http://ohsr.od.nih.gov/guidelines/nuremberg.html)

29. Declaration of Helsinki. (Accessed at: http://ohsr.od.nih.gov/guidelines/helsinki.html)

30. Belmont report. (Accessed at: http://ohsr.od.nih.gov/guidelines/belmont.html)

31. ICH E6(R1) – Guideline for Good Clinical Practice. June 1996. (Accessed at: www.ich.org/LOB/media/MED/A482.pdf)

32. Barnes M, Heffernan K. The "Future Uses" Dilemma: Secondary Uses of Data and Materials by Researchers for Commercial Research Sponsors. Medical Research Law & Policy, 2004; 3: 440-450.

33. Eriksson S, Helgesson G. Potential harms, anonymization, and the right to withdraw consent to biobank research. Eur J Hum Genet., 2005; 13:1071-1076. (Accessed at: www.nature.com/ejhg/journal/v13/n9/pdf/5201458a.pdf)

34. Renegar G, Webster CJ, Stuerzebecher S, et al. Returning genetic research results to individuals: points-to-consider. Bioethics 2006; 20: 24-36. (Accessed at: http://www3.interscience.wiley.com/cgi-bin/fulltext/118562753/PDFSTART)

35. Article 29 Data Protection Working Party. (Accessed at: www.ec.europa.eu/justice_home/fsj/privacy/workinggroup/index_en.htm)

36. Human Tissue Act 2004 (UK). (Accessed at: www.opsi.gov.uk/acts/acts2004/en/ukpgaen_20040030_en_1)

37. Genetic Information Nondiscrimination Act. (Accessed at: http://webgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=110_cong_public_laws&docid=f:pu0233.110.pdf)

38. Guidance for Sponsors, Clinical Investigators, and IRBs Data Retention When Subjects Withdraw from FDA-Regulated Clinical Trials. FDA October 2008 www.fda.gov/OHRMS/DOCKETS/98fr/FDA-2008-D-0576-gdl.pdf

39. Anderson C, Gomez-Mancilla B, Spear BB, Barnes DM, Cheeseman K, Shaw P, Friedman J, McCarthy A, Brazell C, Ray SC, McHale D, Hashimoto L, Sandbrink R, Watson ML, Salerno RA, on behalf of The Pharmacogenetics Working Group. Elements of Informed Consent for Pharmacogenetic Research: Perspective of the Pharmacogenetics Working Group. Pharmacogenomics Journal 2002;2:284-92. (Accessed at: www.nature.com/tpj/journal/v2/n5/abs/6500131a.html)


www.i-pwg.org

12.4 Abbreviations

Abbreviation/Term	Definition
1L	First Line
2L	Second Line
5-FU	5-fluorouracil
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
AUC	Area Under the Curve
BICR	Blinded independent central review
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
CTFG	Clinical Trial Facilitation Group
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
EOC	Executive Oversight Committee
EORTC	European Organisation for Research and Treatment of Cancer
ePRO	Electronic Patient Reported Outcomes
ERC	Ethics Review Committee
FBR	Future Biomedical Research
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FDAMA	Food and Drug Administration Modernization Act
FNA	Fine Needle Aspirate

Abbreviation/Term	Definition
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
HBsAg	Hepatitis B surface Antigen
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HNSCC	Head and Neck Squamous Cell Carcinoma
HPV	Human Papillomavirus
IA1	Interim analysis 1
IA2	Interim analysis 2
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
mAb	Monoclonal Antibody
mcL	Microliters
MEL	Melanoma
Mg	Milligram
Mg/kg	Milligram per Kilogram
mL	milliliter
MRI	Magnetic Resonance Imaging
MSD	Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
MTD	Maximum Tolerated Dose
NA or N/A	Not Applicable
NCI	National Cancer Institute
NPV	Negative Predictive Value
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

Abbreviation/Term	Definition
PH	Proportional Hazard
PIN	Personal Identification Number
PK	Pharmacokinetic
PK/PD	Pharmacokinetic/Pharmacodynamic
PO	Oral Administration
PPV	Positive Predictive Value
PR	Partial Response
PS	Performance Status
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
QoL	Quality of Life
R/M	Recurrent or Metastatic
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic Acid
ROW	Rest of World
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
sSAP	Supplemental statistical analysis plan
SOP	Standard Operating Procedures
TPS	Tumor Proportion Score
TRAE	Treatment Related Adverse Event
TSH	Thyroid Stimulating Hormone
TTD	Time to Deterioration
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.

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	