SPONSOR: The University of Texas MD Anderson Cancer Center (IND Office)

TITLE: Personalized, randomized, phase 2 study of pembrolizumab (MK-3475) for high risk oral intra-epithelial neoplasias

IND NUMBER: TBD

CONTENTS

1.0 TRIAL SUMMARY

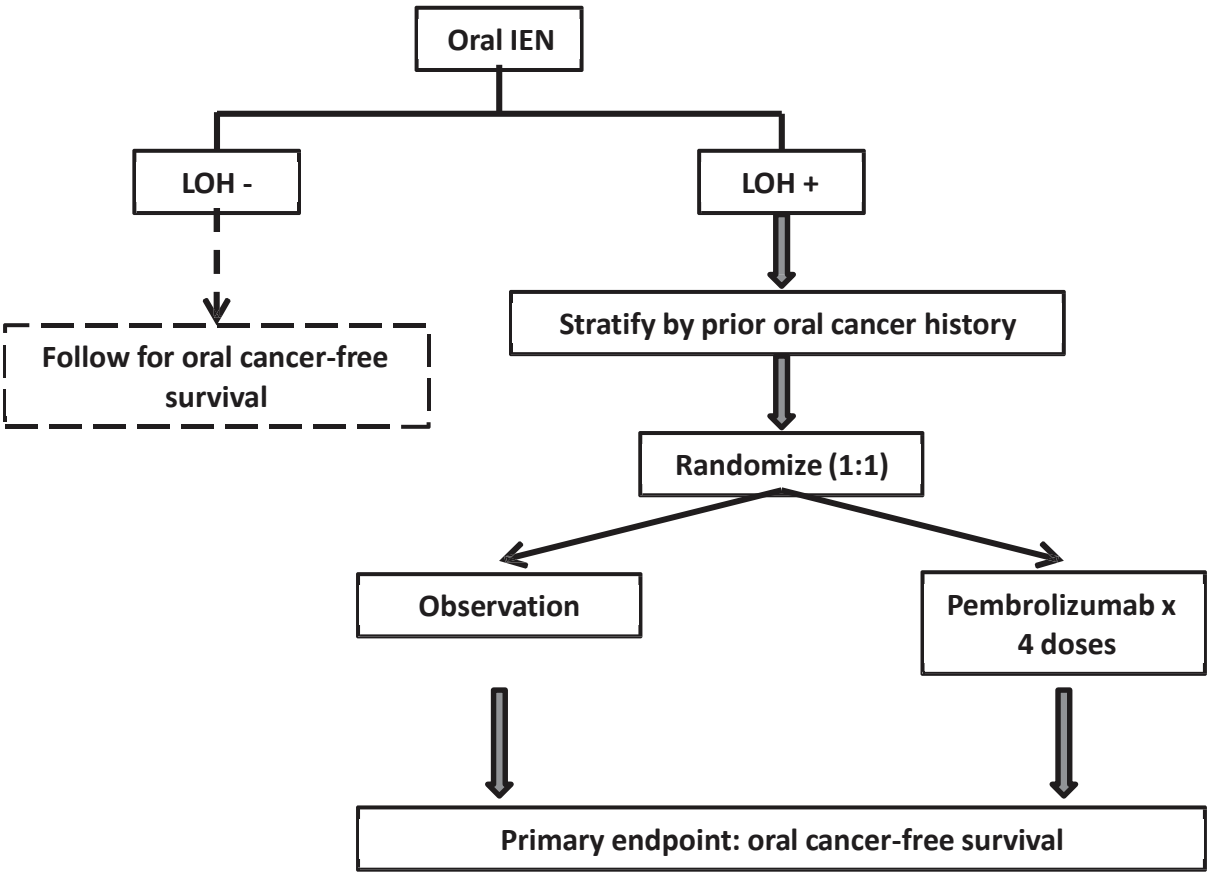
Abbreviated Title	Pembrolizumab for oral IEN
Trial Phase	II
Clinical Indication	Oral intra-epithelial neoplasias
Trial Type	Randomized
Type of control	N/A
Route of administration	Intravenous
Trial Blinding	Open label
Treatment Groups	Control: no treatment Experimental: pembrolizumab
Number of trial subjects	104 randomized (approximately 250 screened)
Estimated enrollment period	48 months
Estimated duration of trial	84 months
Duration of Participation	36 months

2.1 TRIAL DESIGN

2.2 Trial Design

This is a randomized, single-institution, open-label, phase 2 trial of pembrolizumab versus observation in patients with histologically-proven oral intra-epithelial neoplasias (IEN) molecularly defined as high risk by the presence of specific loss of heterozygosity (LOH) profiles.

2.3 Trial Diagram



3.1 OBJECTIVE(S) & HYPOTHESIS(ES)

3.2 Primary Objective(s) & Hypothesis(es)

(1) **Objective:** To determine oral cancer-free survival of patients with high risk oral IEN treated with pembrolizumab versus observation

Hypothesis: In individuals with high risk oral IEN, pembrolizumab will improve oral cancer-free survival compared to observation

3.3 Secondary Objective(s) & Hypothesis(es)

(2) **Objective**: To determine safety and tolerability of pembrolizumab for patients with oral IEN

Hypothesis: Pembrolizumab will have similar or better toxicity profile as in patients with advanced cancers

(3) **Objective**: To determine the histologic and clinical response rates (in the subgroup of patients with clinically evident, measurable oral IEN lesions) to pembrolizumab

Hypothesis: Pembrolizumab will reverse histologic changes associated with oral IEN, and will reduce the size of clinically evident oral IEN lesions (i.e., leukoplakia and/or erythroplakia)

(4) **Objective**: To characterize the immune infiltrate in oral IEN lesions before and after treatment with pembrolizumab.

Hypothesis: Pembrolizumab will stimulate a specific, monoclonal / oligoclonal adaptive immune response

3.4 Exploratory Objective

(5) **Objective**: To assess predictive, tissue- and blood-based, biomarkers of benefit from pembrolizumab in oral IEN.

Hypothesis: Analysis of tissue and blood biomarkers before and after treatment may identify predictive markers of benefit from pembrolizumab and will increase the understanding of the immune biology of oral IEN that could lead to enhanced mechanisms of immune evasion and resistance to pembrolizumab.

(6) **Objective**: To determine the presence of neo-antigens in IEN lesions before and after treatment, and their correlation with oral cancer-free survival and immune infiltrate characteristics.

Hypothesis: IEN will have somatic mutations that lead to development of neo-antigens that could be related to benefit from pembrolizumab.

(7) **Objective**: To evaluate the oral micro-biome before and after treatment with pembrolizumab and its association with neo-antigens and benefit from treatment.

Hypothesis: Oral microbiome may modulate the immune function in the oral epithelium and may influence benefit from immune checkpoint inhibitors.

4.1 BACKGROUND & RATIONALE

4.2 Background

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

4.1.1 Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells / FoxP3+ regulatory T-cells seems to correlate with improved prognosis and long-term survival in many solid tumors.

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an Ig superfamily member related to CD28 and CTLA-4 which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2). The structure of murine PD-1 has been resolved. 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. 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. 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. Expression has also been shown during thymic development on CD4- CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells. 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 . 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. 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). This suggests that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention.

Pembrolizumab 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. Keytruda™ (pembrolizumab) has recently been approved in the United States for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilumumab and, if BRAF V600 mutation positive, a BRAF inhibitor.

4.1.2 Preclinical and Clinical Trial Data

Refer to the Investigator's Brochure for Preclinical and Clinical data.

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

Oral pre-malignant lesions, or intra-epithelial neoplasias (IEN), are in and of themselves markers of oral cancer risk. Clinically, they are often recognized as leukoplakia and/or erythroplakia. Histologically, they are often characterized as hyperplasia/hyperkeratosis, mild, moderate and/or severe dysplasia / carcinoma in situ.[1]

Despite extensive investigations, a drug that can be used as standard of care to treat oral IEN and/or to reduce cancer incidence in patients with oral IEN is yet to be developed.[1]

The need for novel trial designs to successfully develop drugs for management oral IEN has recently been highlighted.[1-3] This includes (a) the use of convergent trial designs,[4] (b) focus on high risk populations,[3] (c) identification of intermediary endpoints related to the biology of the agent used in earlier-stage trials that can inform subsequent larger-scale studies and novel strategies,[3,5] (d) reverse migration of active agents from use in advanced cancers settings to pre-malignant lesion settings.[6]

Convergent trial designs recognize that IEN and early stage invasive cancers share common pathogenesis. Therefore, patients with oral IEN lesions and curatively treated (resected) oral cancers may exhibit similar, increased risk of developing a primary invasive oral cancer, a second primary tumor, or recurrence. This is especially true for molecularly defined, high risk subgroups. As such, modern trials can combine patients with high risk IEN that may or may not have had a prior history of oral cancer, in designs that converge prevention and adjuvant therapy to understand the molecular biology of candidate therapeutic agents and their ability to reduce subsequent cancer development.[4] Specific to oral IEN, high risk groups can be molecularly defined as IEN exhibiting high risk LOH profiles (i.e., LOH positive group).[7-11]

High risk LOH profiles in oral IEN (including LOH at 3p14 and/or 9p21) have been recognized as a molecular marker that can predict oral cancer development in patients with or without a prior history of oral cancer in case-control studies.[7-10] In a recently completed study led by MD Anderson (the Erlotinib Prevention of Oral Cancer [EPOC] trial), these observations were confirmed for the first time, in a prospective way, within the context of a large-scale clinical trial, paving the way for personalized, molecularly-based IEN treatment.[11] LOH is now considered the most robust prognostic marker of cancer risk in oral IEN.

In EPOC, patients with histological evidence of oral IEN (with or without a prior history of oral cancer) had their lesions evaluated for LOH profiles. LOH negative patients did not receive any treatment and were followed for oral cancer development. Only the LOH positive patients continued with randomization on study to treatment with erlotinib versus placebo for one year, with the primary endpoint of oral cancer-free survival. Over approximately 5.5 years, 398 patients were screened for LOH within the context of EPOC. LOH was positive in 68% of the patients, and 150 patients were randomized to erlotinib versus placebo. The 3-year oral cancer-free survival for the LOH positive group was 76%, versus 87% for the LOH

negative patients (HR=2.1; 95% CI 1.17 – 3.78, p=0.01). Erlotinib did not improve the primary endpoint of oral cancer-free survival (HR=1.23; 95% CI 0.66-2.23; p=0.51).[11]

These findings support focusing on LOH positive patients when studying a high cancer risk population with oral IEN, and allow for the design of a clinical trial with a definitive endpoint of oral cancer with a relatively small sample size. Additionally, the focus on high risk subgroups potentially improves the benefit-risk, and benefit-cost ratio of the intervention studied, by enrolling a population with a high number of events, for whom pharmacologic intervention would be reasonable, even if associated with mild to moderate toxicities.

Pembrolizumab has shown durable activity, with short-term onset, in patients with metastatic head and neck squamous cell carcinomas, with a favorable side effect profile.[12] In this clinical trial, 51% of the patients had some degree of decrease in tumor burden, and a response rate according to RECIST 1.1 of 19.6%. As such, pembrolizumab may be considered an ideal candidate be studied for cancer risk reduction in oral IEN, following the aforementioned convergent trial design and reverse migration principles of drug development for IEN.

4.2.2 Rationale for Dose Selection/Regimen/Modification

An open-label Phase I trial (Protocol 001) evaluated the safety and clinical activity of single agent MK-3475. The dose escalation portion of this trial evaluated three dose levels, 1 mg/kg, 3 mg/kg, and 10 mg/kg, administered every 2 weeks (Q2W) in subjects with advanced solid tumors. All three dose levels were well tolerated and no dose-limiting toxicities were observed. This first in human study of MK-3475 showed evidence of target engagement and objective evidence of tumor size reduction at all dose levels (1 mg/kg, 3 mg/kg and 10 mg/kg Q2W). No MTD has been identified. Recent data from other clinical studies within the MK-3475 program has shown that a lower dose of MK-3475 and a less frequent schedule may be sufficient for target engagement and clinical activity.

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

A population pharmacokinetic analysis has been performed using serum concentration time data from 476 patients. Within the resulting population PK model, clearance and volume parameters of MK-3475 were found to be dependent on body weight. The relationship between clearance and body weight, with an allometric exponent of 0.59, is within the range observed for other antibodies and would support both body weight normalized dosing or a fixed dose across all body weights. MK-3475 has been found to have a wide therapeutic range based on the melanoma indication. The differences in exposure for a 200 mg fixed dose regimen relative to a 2 mg/kg Q3W body weight based regimen are anticipated to remain well within the established exposure margins of 0.5 – 5.0 for MK-3475 in the melanoma indication. The exposure margins are based on the notion of similar efficacy and safety in melanoma at 10 mg/kg Q3W vs. the proposed dose regimen of 2 mg/kg Q3W (i.e.

5-fold higher dose and exposure). The population PK evaluation revealed that there was no significant impact of tumor burden on exposure. In addition, exposure was similar between the NSCLC and melanoma indications. Therefore, there are no anticipated changes in exposure between different indication settings.

The rationale for further exploration of 200 mg Q3W of pembrolizumab is based on: 1) similar efficacy and safety of pembrolizumab when dosed at either 2 mg/kg or 10 mg/kg Q3W in melanoma patients, 2) the flat exposure-response relationships of pembrolizumab for both efficacy and safety in the dose ranges of 2 mg/kg Q3W to 10 mg/kg Q3W, 3) the lack of effect of tumor burden or indication on distribution behavior of pembrolizumab (as assessed by the population PK model) and 4) the assumption that the dynamics of pembrolizumab target engagement will not vary meaningfully with tumor type.

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

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

4.2.3 Rationale for Endpoints

4.2.3.1 Efficacy Endpoints

Surrogate markers to assess efficacy of treatment in individuals with oral IEN are yet to be developed. Clinical and/or histological response of IEN to interventions only marginally correlate with long term oral cancer-free survival.[5,13] While a study focusing on short-term responses would have an early readout, there is concern that response rates would inaccurately ascertain the efficacy of the agent. As such, the definitive endpoint of oral cancer-free survival was selected for this trial, in order to truly evaluate the possible effects of pembrolizumab in reducing development of invasive cancer. Because a high risk population is targeted for this study, with an expected relatively high number of events, the choice of oral cancer-free survival as an endpoint is still feasible with a reasonable sample size. Clinical and histologic response rates have been selected as secondary endpoints so that the immediate effects of the intervention on oral IEN can be determined, and their associations with long-term oral cancer-free survival can be studied.

4.2.3.2 Biomarker Research

There is substantial interest in identifying biomarkers predictive of response to immune checkpoint inhibitors in invasive solid tumors and the same principles apply to the setting of

oral intra-epithelial neoplasias. Furthermore, the interactions of non-invasive lesions with the immune system, microbiome, and genetic and epigenetic changes in the epithelium, and how they are influenced by PD-1 blockade are largely unknown. As such, the biomarkers to be evaluated on this study aim at:

(1) understanding the risk of malignant transformation in individuals exposed or not to pembrolizumab, thus providing novel prognostic markers for risk assessment

(2) identifying the population more likely to benefit from pembrolizumab

(3) characterizing the immune response in the setting of non-invasive lesions, before and after treatment

(4) evaluating the interplay between the immune system, the microbiome, the non-invasive epithelial lesions, and their genetic, epigenetic, transcriptomic and phenotypic changes before and after treatment with pembrolizumab.

Because the biomarker research embedded in this protocol is exploratory, a broad panel of makers will be studied, utilizing the most updated knowledge from other clinical and pre-clinical studies related to the biology of IEN and immune checkpoint blockade at the time of the analysis.

4.2.4 Risk / benefit ratio

This protocol has been carefully designed to optimize the risk / benefit ratio, as outlined below:

(a) Selection of a high risk patient population. The 3-, 4- and 5-year risk of developing oral cancer in LOH positive individuals is estimated at 76%, 70%, and 65%, as observed in the EPOC trial.[11] Furthermore, without any intervention, it has been demonstrated that the oral cancer risk in individuals with IEN will not diminish with time, thus leading to increased cumulative incidence of oral cancer long-term.[9] It should be noted that a 65% 5-year cancer-free survival is compatible with the 5-year recurrence-free survival of stage IIIA melanoma patients (63% in the study by Romano et al.[14]), who are included in the ongoing randomized phase III trial of adjuvant pembrolizumab conducted by the European Organization for Research and Treatment of Cancer (NCT02362594).

(b) Selection of oral cancer-free survival as the primary endpoint. Treatment of oral cancers entails glossectomies, oftentimes followed by radiation therapy or chemo-radiation therapy, that may result in functional disabilities (e.g., dysarthria, dysphagia) and other treatment-related complications (e.g., microaspiration and pneumonias, radiation-induced carotid artery stenosis, cisplatin-induced neuropathies, renal failure and ototoxicity). As such, a reduction in the incidence of oral cancer may lead to lesser need for therapeutic interventions, possibly improving functional outcomes.

(c) Selection of an immunotherapy drug with a favorable adverse event profile. In contrast to anti-CTLA4 drug ipilimumab, the anti-PD-1 antibody pembrolizumab has been shown to have a more favorable adverse event profile.[15] In randomized studies comparing pembrolizuamb to docetaxel, pembrolizumab was also found to have a lower incidence of toxic effects.[16] The tables below outline the incidence of adverse events associated with pembrolizumab single agent in a clinical trial including 550 non-small cell lung cancer patients (an FDA-approved indication for the drug). The overall incidence of grade 3-5 adverse events was 9.5%. While severe immune-mediated adverse events may occur, the incidence was low (3.8% grade 3-5), fatalities were extremely rare (0.2%), and the vast majority of patients (69.3%) exhibited complete resolution of toxicities to grade 0.

Immune-Mediated AE Summary in patients with metastatic non-small cell lung cancer treated with pembrolizumab in the KEYNOTE-001 study

Category	Total N-550
Any, n (%)	80 (14.5)
Grade ≥3, n (%)	21 (3.8)
Led to death [a], n (%)	1 (0.2)
Led to discontinuation, n (%)	15 (2.7)
Events resolved [b, c], %	69.3

[a]Pneumonitis. [b]includes all events of any grade, excluding hypothyroidism. [c]Resolution is defined as a return to grade 0 or baseline. Data cutoff date: January 23, 2015

Adverse Events in Patients with Non-small Cell Lung Cancer Treated with Pembrolizumab in KEYNOTE-001*

Adverse Events	Any Grade	Grade 3-5
	no. of patients (%) N=495 total patients	
Fatigue	96 (19.4)	4 (0.8)
Pruritus	53 (10.7)	0
Decreased appetite	52 (10.5)	5 (1.0)
Rash	48 (9.7)	1 (0.2)
Arthralgia	45 (9.1)	2 (0.4)
Diarrhea	40 (8.1)	3 (0.6)
Nausea	37 (7.5)	4 (0.8)
Hypothyroidism	34 (6.9)	1 (0.2)
Asthenia	24 (4.8)	5 (1.0)
Anemia	21 (4.2)	0
Dyspnea	21 (4.2)	19 (3.8)
Pyrexia	21 (4.2)	3 (0.6)
Decreased weight	19 (3.8)	2 (0.4)
Dry skin	18 (3.6)	0
Pneumonitis†	18 (3.6)	9 (1.8)
Elevation in aspartate aminotransferase	15 (3.0)	3 (0.6)
Vomiting	14 (2.8)	3 (0.6)
Dermatitis acneiform	13 (2.6)	0
Myalgia	13 (2.6)	0
Cough	12 (2.4)	0
Elevation in alanine aminotransferase	11 (2.2)	2 (0.4)
Chills	10 (2.0)	0
Constipation	10 (2.0)	2 (0.4)
Infusion-related reaction	15 (3.0)	1 (0.2)

* Listed are events that were considered to be related to treatment by the investigator and were reported in at least 2% of patients.
† Included among patients with pneumonitis is one patient with grade 5 interstitial lung disease.

(d) Selection of a short treatment course. The three-month treatment period utilized within this protocol is likely to reduce the incidence of adverse events and/or limit their duration.

5.1 METHODOLOGY

5.2 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

Histological evidence of oral intra-epithelial neoplasia within 12 months prior to enrollment. Subjects with a history or clinical diagnosis suggestive of oral intra-epithelial neoplasia, or patients with a history of invasive oral cancer are eligible, but must have a confirmed histological diagnosis of oral intra-epithelial neoplasia before randomization. Histological evidence of oral intraepithelial neoplasia on an invasive oral cancer resection specimen is acceptable.

A visible, measurable, clinical lesion (such as leukoplakia and/or erythroplakia) is not required.

Loss of heterozygosity (LOH) profiles will be determined in the oral intra-epithelial neoplasia lesion in a CLIA-certified lab, and 2described in sections 5.1.2 and 5.1.3. High risk LOH profiles (i.e., LOH positive cases) are defined as follows:

Patients without a prior oral cancer history: LOH at 3p14 and/or 9p21 plus at least at one additional chromosomal site (4q, 8p, 11p, 13q, or 17p)

Patients with a prior oral cancer history: LOH at 3p14 and/or 9p21

5.1.2 Subject Inclusion Criteria for Randomization

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

1. Be willing and able to provide written informed consent for the trial.
2. Be ≥ 18 years of age on day of signing informed consent.
3. Be willing to provide tissue from a newly obtained oral biopsy.
4. Have a performance status of 0-2 on the ECOG Performance Scale.
5. Demonstrate adequate organ function as defined in Table 1
6. Table 1 Adequate Organ Function Laboratory Values

System	Laboratory Value

Hematological	
Absolute neutrophil count (ANC)	≥1,500 /mcL
Platelets	≥75,000 / mcL
Hepatic	
Serum total bilirubin	≤ 1.5 X ULN **OR**
	Direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 X ULN

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

8. 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 study therapy through 120 days after the last dose of study medication (Reference Section 5.7.2). Subjects of childbearing potential are those who have not been surgically sterilized or have not been free from menses for > 1 year.

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

5.1.3 Subject Exclusion Criteria for Randomization

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

1. Is currently participating and receiving study therapy with potential anti-neoplastic activity, or has participated in a study of an investigational agent and received study therapy with potential anti-neoplastic activity within 4 weeks of the first dose of treatment.

2. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment.

3. Has a known history of active TB (Bacillus Tuberculosis)

4. Hypersensitivity to pembrolizumab or any of its excipients.

5. Has had a prior anti-cancer monoclonal antibody (mAb) within 4 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 2 or at baseline) from adverse events due to agents administered more than 4 weeks earlier.

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

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

7. Has a known additional malignancy that is progressing or requires active treatment other than adjuvant hormonal therapy. Exceptions include basal cell carcinoma of the skin or squamous cell carcinoma of the skin or in situ cervical cancer.

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

9. Has known history of, or any evidence of active, non-infectious pneumonitis.

10. Has an active infection requiring systemic therapy.

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

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

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

14. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent.

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

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

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

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

5.2 Trial Treatments

The treatment to be used in this trial is outlined below in Table 2 and will be only be administered to subjects randomized to the experimental arm.

Table 2 Trial Treatment

Drug	Dose	Dose Frequency	Route of Administration	Number of doses	Treatment group
Pembrolizumab	200 mg	Q3W	IV infusion	4	Experimental

5.2.1 Dose Selection/Modification

5.2.1.1 Dose Selection

The rationale for selection of doses to be used in this trial is provided in Section 4.0 – Background and Rationale.

Details on preparation and administration of pembrolizumab (MK-3475) are provided in the Pharmacy Manual.

5.2.1.2 Dose Modification

Adverse events (both non-serious and serious) associated with pembrolizumab exposure may represent an immunologic etiology. These adverse events may occur shortly after the first dose or several months after the last dose of treatment. Pembrolizumab must be withheld for drug-related toxicities and severe or life-threatening AEs as per Table 3 below. See Section 5.6.1 and Events of Clinical Interest Guidance Document for supportive care guidelines, including use of corticosteroids.

Table 3

Dose Modification Guidelines for Drug-Related Adverse Events

Toxicity	**Hold Treatment For Grade**	**Timing for Restarting Treatment**	**Discontinue Subject**
Diarrhea/Colitis	2-3	Toxicity resolves to Grade 0-1.	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue
AST, ALT, or Increased Bilirubin	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose.
	3-4	Permanently discontinue (see exception below)[1]	Permanently discontinue
Type 1 diabetes mellitus (if new onset) or	T1DM or 3-4	Hold pembrolizumab for new onset Type 1 diabetes mellitus or Grade 3-4 hyperglycemia associated with evidence of	Resume pembrolizumab when patients are clinically and metabolically stable.

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Discontinue Subject
Hyperglycemia		beta cell failure.	
Hypophysitis	2-3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue
Hyperthyroidism	3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue
Hypothyroidism	2-4	Therapy with pembrolizumab can be continued while treatment for the thyroid disorder is instituted	Therapy with pembrolizumab can be continued while treatment for the thyroid disorder is instituted.
Infusion Reaction	3-4	Permanently discontinue	Permanently discontinue
Pneumonitis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	3-4	Permanently discontinue	Permanently discontinue
Renal Failure or Nephritis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	3-4	Permanently discontinue	Permanently discontinue
All Other Drug-Related Toxicity[2]	3 or Severe	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue

Note: Permanently discontinue for any severe or Grade 3 drug-related AE that recurs or any life-threatening event.
[1] For patients with liver metastasis who begin treatment with Grade 2 AST or ALT, if AST or ALT increases by greater than or equal to 50% relative to baseline and lasts for at least 1 week then patients should be discontinued.
[2] Patients with intolerable or persistent Grade 2 drug-related AE may hold study medication at physician discretion. Permanently discontinue study drug for persistent Grade 2 adverse reactions for which treatment with study drug has been held, that do not recover to Grade 0-1 within 12 weeks of the last dose.

Dosing interruptions are permitted in the case of medical / surgical events or logistical reasons not related to study therapy (e.g., elective surgery, unrelated medical events, patient vacation, and/or holidays). Subjects should be placed back on study therapy within 6 weeks of the scheduled interruption, unless otherwise discussed with the Principal Investigator. The reason for interruption should be documented in the patient's chart. There will be no dose reduction permitted in this study.

5.2.2 Timing of Dose Administration

Trial treatment should be administered on Day 1 of each cycle after all procedures/assessments have been completed as detailed on the Trial Flow Chart (Section 6.0). Trial treatment may be administered up to 7 days before or after the scheduled Day 1 of each cycle.

All trial treatments will be administered on an outpatient basis.

Pembrolizumab 200 mg will be administered as a 30 minute IV infusion.

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

5.2.3 Trial Blinding/Masking

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

5.3 Randomization or Treatment Allocation

Patients seeking treatment at MD Anderson will be screened for this trial, including patients with oral cancers or oral IEN treated or followed at the MD Anderson Head and Neck Center. Subjects may also be identified at the multidisciplinary planning conferences, or through databases maintained by the Head and Neck Program for quality improvement. Patients in these databases who have a diagnosis of oral IEN or oral cancer may be contacted by phone or mail or during their clinic visits at MD Anderson to offer participation in the study.

Study-related procedures must not commence before obtaining consent. However, results from assessments performed before obtaining informed consent that are considered "routine standard of care" (e.g., laboratory results, CT scans, etc.) may be used to determine eligibility.

Once consent is obtained, oral IEN LOH evaluation will be performed in an archival tissue specimen obtain within 12 months prior to enrollment, or in a newly obtained oral tissue specimen. Subjects do not need to meet the eligibility criteria described in sections 5.1.2 and 5.1.3 to have their tissue evaluated for LOH. LOH negative patients will continue to be observed and followed for oral cancer-free survival, but will not be eligible for treatment or randomization. Only LOH positive cases will be eligible for randomization. Patients must also meet the additional eligibility criteria described in sections 5.1.2 and 5.1.3 to be eligible for randomization.

Randomization will be performed via a centralized, web-based randomization system. Stratified randomization with dynamic allocation will be performed via the web-based database system. For randomization purposes, eligible patients will be stratified by prior cancer status (no prior cancer versus prior cancer). Within each stratum, Pocock-Simon dynamic allocation method will be applied to achieve balanced randomization with respect to smoking status (current, former and never smoker). Patients will be randomized into the pembrolizumab arm or the observation arm with equal probability. A randomization algorithm will be developed and implemented by the department of Biostatistics at M.
D. Anderson Cancer Center. Patients who are randomized will be given a unique patient number by the centralized, web-based system and assigned to a treatment arm as follows:

Arm A (Control): observation

Arm B (Experimental): pembrolizumab

5.4 Stratification

The following stratification factors will be utilized:

- Prior history of oral cancer: yes or no

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 one of these or other medications or vaccinations specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary physician.

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 patient's electronic medical record.

5.5.2 Prohibited Concomitant Medications

Subjects are prohibited from receiving the following therapies during the Treatment Phase of this trial:

- Antineoplastic systemic chemotherapy or biological therapy (with the exception of adjuvant hormonal therapy)
- Immunotherapy not specified in this protocol
- Investigational agents with anti-neoplastic activity other than pembrolizumab
- Radiation therapy
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine.

- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Principal Investigator.

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

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

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

5.6 Rescue Medications & Supportive Care

5.6.1 Supportive Care Guidelines

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

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

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

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

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

- All subjects who experience diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion. For Grade 2 or higher diarrhea, consider GI consultation and endoscopy to confirm or rule out colitis.
- For **Grade 2 diarrhea/colitis** that persists greater than 3 days, administer oral corticosteroids.
- For **Grade 3 or 4 diarrhea/colitis** that persists > 1 week, treat with intravenous steroids followed by high dose oral steroids.
- When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

- **Type 1 diabetes mellitus (if new onset, including diabetic ketoacidosis [DKA]) or ≥ Grade 3 Hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA)**

  - For **T1DM** or **Grade 3-4** Hyperglycemia
    - Insulin replacement therapy is recommended for Type I diabetes mellitus and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria.
    - Evaluate patients with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.

- **Hypophysitis**:

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

- **Hyperthyroidism or Hypothyroidism**:
  Thyroid disorders can occur at any time during treatment. Monitor patients for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders.

  - **Grade 2** hyperthyroidism events (and **Grade 2-4** hypothyroidism):
    - In hyperthyroidism, non-selective beta-blockers (e.g. propranolol) are suggested as initial therapy.

    - In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or 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 4 below shows treatment guidelines for subjects who experience an infusion reaction associated with administration of pembrolizumab (MK-3475).

Table 4 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

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 hrs	**Stop Infusion and monitor symptoms.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. **Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.**	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab (MK-3475) with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **Subject is permanently discontinued from further trial treatment administration.**	No subsequent dosing
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.		

5.7 Diet/Activity/Other Considerations

5.7.1 Diet

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

5.7.2 Contraception

Pembrolizumab may have adverse effects on a fetus in utero. Furthermore, it is not known if pembrolizumab has transient adverse effects on the composition of sperm. Non-pregnant, non-breast-feeding women may be enrolled if they are willing to use 2 methods of birth

control or are considered highly unlikely to conceive. Highly unlikely to conceive is defined as 1) surgically sterilized, or 2) postmenopausal (a woman who is ≥45 years of age and has not had menses for greater than 1 year will be considered postmenopausal), or 3) not heterosexually active for the duration of the study. The two birth control methods can be either two barrier methods or a barrier method plus a hormonal method to prevent pregnancy. Subjects should use birth control for up to 120 days after the last dose of study therapy.

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

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

5.7.3 Use in Pregnancy

If a subject inadvertently becomes pregnant while on treatment with pembrolizumab, the subject will immediately discontinue treatment. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been completed or terminated.

5.7.4 Use in Nursing Women

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

5.8 Criteria for Subject Withdrawal/Discontinuation from Study

Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the investigator or the IND Office if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding discontinuation or withdrawal are provided below.

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

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

- Investigator's decision to withdraw the subject
- Administrative reasons

5.8.1 Discontinuation of Study Therapy

Subjects must discontinue therapy for the following reasons:

- Withdrawal / discontinuation from study.
- Worsening oral lesions requiring discontinuation from study therapy, in the opinion of the treating physician
- Unacceptable adverse experiences as described in Section 5.2.1.2
- Intercurrent illness that prevents further administration of treatment
- Investigator's or patient's decision
- The subject has a confirmed positive serum pregnancy test
- Development of oral cancer
- The subject is lost to follow-up

For patients that develop oral cancer during the study or for patients that are lost to follow up, only the procedures described under "Lon-Term Follow-Up" in section 6.0 will be performed.

If possible, subjects that discontinue therapy before completing 4 cycles of treatment should remain on study and continue to undergo study procedures and follow-ups as described in Section 6.0.

5.9 Subject Replacement Strategy

Efficacy analysis on this trial will be per intent-to-treat. As such, there will be no replacement for subjects that are randomized, but do not initiate and/or complete study procedures and treatments.

5.10 Clinical Criteria for Early Trial Termination

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

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

2. Poor adherence to protocol and regulatory requirements

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

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

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

6.1 TRIAL FLOW CHART

6.2 Study Flow Chart

Trial Period:	Screening Phase		Treatment Cycles[a]				Follow-Up								Long-Term Follow-Up
Treatment Cycle/Title:	Pre-screening (Visit 1)	Main Study Screening (Visit 2)	1	2	3	4	End of Treatment / Re-evaluation	Post-treatment							As needed for trial data interpretation throughout and after the study period as determined by the Principal Investigator
Scheduling Window (Days):		-28 to -1 days	Week (± 7 days)[b] 1	4	7	10	Month 3 ± 7 days[c]	Month (± 1 month) 6	9	12	Month (± 2 months) 18	24	30	36	
Administrative Procedures															
Informed Consent	X														
LOH evaluation	X														
Tobacco and alcohol use history	X						X	X	X	X	X	X	X	X	
Prior oral cancer history	X														
Inclusion/Exclusion Criteria		X													
Demographics and Medical History		X													
Concomitant Medication Review		X													
Trial Treatment Administration			X	X	X	X									
Oral Cancer-free Survival Status															X
Clinical Procedures/Assessments															
Review Adverse Events		X		X	X	X	X[a]								
Physical Examination		X		X	X	X	X	X	X	X	X	X	X	X	
ECOG Performance Status		X													
Laboratory Procedures/Assessments: analysis performed by LOCAL laboratory															
Pregnancy Test – Urine or Serum -HCG		X[a]					X[a]								
Urinalysis		X					X[a]								
CBC with Differential		X		X	X	X	X	X[a]		X					
Comprehensive Serum Chemistry Panel		X		X	X	X	X	X[a]		X					
T3, FT4 and TSH		X					X[a]	X[a]							
Non-invasive Efficacy Measurements															
Oral lesion measurement		X					X			X					
Tumor Biopsies/Archival Tissue Collection/Correlative Studies Blood and Oral Swab															

Trial Period:	**Screening Phase**		**Treatment Cycles[a]**				**Follow-Up**								**Long-Term Follow-Up**
Treatment Cycle/Title:	Pre-screening (Visit 1)	Main Study Screening (Visit 2)	1	2	3	4	End of Treatment / Re-evaluation	Post-treatment							As needed for trial data interpretation throughout and after the study period as determined by the Principal Investigator
Scheduling Window (Days):		-28 to -1 days	Week (± 7 days)[b]				Month 3 ± 7 days[c]	Month (± 1 month)			Month (± 2 months)				
			1	4	7	10		6	9	12	18	24	30	36	
Archival or Newly Obtained Tissue Collection[d]	X														
Newly Obtained Tissue Collection		X[e]					X			X					
Correlative Studies Blood Collection[f]	X			X			X			X				X	
Oral Swab Collection[f]	X			X			X			X				X	

[a] To be performed only in subjects randomized to the experimental arm. Pregnancy test must be performed <72 hours prior to the first dose of study medication.

[b] If there are treatment delays, timing of subsequent cycles will be adjusted so that pembrolizumab is given every 3 weeks (± 7 days)

[c] In subjects who had a treatment delay, evaluation should be postponed until at least 2 weeks after last dose of treatment

[d] At any time point after enrollment, any archival or newly obtained tissue as part of standard of care for monitoring of oral IEN or newly developed oral cancer may be collected for correlative studies. This applies to any subject participating in the study from the time of enrollment, regardless of LOH or randomization status.

[e] During the screening phase, newly obtained tissue collection may be performed within 12 months before randomization

[f] For patients diagnosed with oral cancer during the study, extra blood collection and oral swabs collection may be performed approximately at the time of diagnosis of invasive cancer.

7.1 TRIAL PROCEDURES

7.2 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 IND Office and/or Merck 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.

Subjects found to be LOH negative, or subjects who are LOH positive but do not undergo randomization for any reason (including declining randomization) will not be removed from the study. However, they will only undergo the study procedures described under "Pre-Screening Visit 1" and "Long Term Follow-up" of the Trial Flow Chart - Section 6.0. Their medical care and follow up will be performed by the treating physicians according to institutional standards. All other subjects should follow the trial procedures according to the Trial Flow Chart - Section 6.0.

7.1.1 Administrative Procedures

7.1.1.1 Informed Consent

The Investigator must obtain documented consent from each potential subject prior to participating in a clinical trial.

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.

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 IND Office requirements.

7.1.1.2 LOH evaluation

LOH evaluation will be performed in a CLIA certified lab in an archival tissue specimen obtained within 12 months prior to enrollment, or in a newly obtained oral tissue specimen. Subjects do not need to meet the eligibility criteria described in sections 5.1.2 and 5.1.3 to have their tissue evaluated for LOH. LOH will be evaluated in the IEN, using peripheral blood as the germline control when necessary.

7.1.1.3 Tobacco and alcohol use history

A detailed tobacco and alcohol use history will be documented in the patient's chart.

7.1.1.4 Prior Oral Cancer History

The prior oral cancer history will be documented in the patient's chart.

7.1.1.5 Inclusion/Exclusion Criteria

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

7.1.1.6 Demographics and Medical History

A medical history will be obtained by the investigator or qualified designee. Details regarding the disease for which the subject has enrolled in this study will be recorded in the electronic medical record.

7.1.1.7 Concomitant Medications Review

Concomitant medications will be documented in the electronic medical record so that the information is available for post-hoc analysis of outcomes related to the study, if relevant. Concomitant medications will not be captured in the electronic trial database.

7.1.1.8 Oral Cancer-Free Survival Status

Information on time to development of oral cancer/disease progression/recurrence, sites of disease, development of second primary tumors, additional therapy, long-term survival, and other relevant clinical data may be obtained throughout and after the study period as deemed necessary by the Principal Investigator for trial data interpretation. Patients (or their family members or designees) may be contacted by telephone or in writing or by electronic mail or during clinic visits during or after treatment discontinuation for collection of oral cancer-survival status. The information may also be obtained through chart reviews.

7.1.2 Clinical Procedures/Assessments

7.1.2.1 Adverse Event (AE) Monitoring

The investigator or qualified designee will be responsible for assigning attribution of adverse events to the study drug. 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 experiences will be graded and recorded according to NCI CTCAE Version 4.0 (see Section 7.2)Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

For subjects receiving treatment with pembrolizumab AEs of unknown etiology associated with pembrolizumab exposure should be evaluated to determine if it is possibly an event of clinical interest (ECI) of a potentially immunologic etiology (termed immune-related adverse events, or irAEs); see the separate ECI guidance document in the Appendix 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

The investigator or qualified designee will perform a physical exam including at least an examination of the oral cavity. Vital signs will be recorded in the patient's chart.

7.1.2.3 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status (see Section 11.1) as specified in the Trial Flow Chart.

7.1.3 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below - Laboratory Safety Evaluations (Hematology, Chemistry).

Laboratory tests for hematology, chemistry, urinalysis, and others are specified in Table 5.

Laboratory tests for Main Study Screening (Visit 2) should be performed within 28 days prior to the first dose of treatment. After Cycle 1, pre-dose laboratory procedures can be conducted up to 72 hours prior to dosing. Results must be reviewed by the investigator or qualified designee and found to be acceptable prior to each dose of trial treatment.

Table 5 Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Urine pregnancy test †	Serum β-human chorionic gonadotropin†
Hemoglobin	Alkaline phosphatase	Urinalysis	(β-hCG)†
Platelet count	Alanine aminotransferase (ALT)		Total thriiodothyronine (T3)
WBC (total and differential)	Aspartate aminotransferase (AST)		Free tyroxine (T4)
Red Blood Cell Count	Lactate dehydrogenase (LDH)		
Absolute Neutrophil Count	Carbon Dioxide ‡		
Absolute Lymphocyte Count	*(CO_2 or biocarbonate)*		
	Uric Acid		
	Calcium		
	Chloride		
	Glucose		
	Phosphorus		
	Potassium		
	Sodium		
	Magnesium		
	Total Bilirubin		
	Direct Bilirubin *(If total bilirubin is elevated above the upper limit of normal)*		
	Total protein		
	Blood Urea Nitrogen		

† Perform on women of childbearing potential only. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required.

‡ If considered standard of care in your region.

7.1.4 Non-invasive Efficacy Measurements

7.1.4.1 Oral lesion measurements

Bi-dimensional measurements of visible oral lesions will be recorded in the patient's chart for assessment of clinical response to treatment (a secondary objective of this study). If no visible oral lesions are present, this will also be recorded in the patient's chart.

7.1.5 Tumor Biopsies/Archival Tissue Collection/Correlative Studies Blood and Oral Swabs

Biospecimens collected (including archival and newly obtained oral tissue, blood, oral swab, and invasive cancer specimens) will be used for LOH evaluation, evaluation of histological response to treatment (a secondary objective of the study), as well as correlative studies. As part of the study, a biospecimen repository will be created. The objective of this repository will be to provide material for future evaluations of other relevant biomarkers that may be associated with clinical outcomes. A written informed consent will be obtained from patients enrolled in this study so that these samples may be analyzed in the future for biomarkers not described in this protocol.

Because the population randomized on this study is considered high risk, oral biopsies performed at baseline, months 3 and 12 are considered standard of care for monitoring for histological progression and invasive cancer development.

Biospecimen collection and handling are described in the Appendix.

The correlative studies to be evaluated in the biospecimens include (but are not limited to):

- expression of PD-L1, PD-L2, B7-H3, B7-x/H4, PD-1, LAG-3, 2B4, BTLA, Tim3 in neoplastic cells, immune cells and epithelium
- expression of CD3, CD4, FoxP3, CD8, CD68, CD57, CD45RO in immune cells
- T cell receptor profiling by massive parallel sequencing, and/or T cell receptor expression assay (DTEA)
- whole exome sequencing to determine presence of neo-antigens
- oral microbiome characterization
- genomic analysis (including genome sequencing and SNP analysis)
- proteomic analysis
- phosphorylation status of multiple kinases (using antibody arrays when appropriate)

- non-coding-RNA and messenger-RNA levels, including the expression signatures interferon gamma, TCR signaling, expanded-immune, de novo.

- identification of sub-populations of T-cells (e.g. CD4+ helper T-cells, CD8+ cytotoxic T-cells, CD4+ CD25+ regulatory T-cells, FOXP3) and myeloid derived suppressor cells (CD19-, CD3-, CD14-, HLADR-, CD11b+, CD33+, CD45+) as well as immune phenotypic markers including ICOS/ICOSL; OX40/OX40-L; 41BB/41BB-L; PD-1/PD-L1 and PD-L2; CD69, and HLA-DR (activation markers that affect T cell function)

- Cytokine profiling

- Pembrolizumab serum levels and anti-pembrolizumab antibodies

- Other biomarkers that may emerge to be important related to the biology of oral IEN and/or pembrolizumab therapy

7.2 Assessing and Recording Adverse Events

7.2.1 Serious Adverse Event Reporting (SAE) Reporting

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or the IND Office, it results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

- Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator, IND Office, and Merck.

- All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in "The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Serious Unanticipated Adverse Events for Drugs and Devices". Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IND Office, regardless of attribution (within 5 working days of knowledge of the event).
- **All life-threatening or fatal events,** that are unexpected, and related to the study drug, must have a written report submitted within **24 hours** (next working day) of knowledge of the event to the Safety Project Manager in the IND Office.
- Unless otherwise noted, the electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MDACC IRB.
- Serious adverse events will be captured from the time of the first protocol-specific intervention, until 30 days after the last dose of drug, unless the participant withdraws consent. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.
- Additionally, any serious adverse events that occur after the 30 day time period that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.

7.2.1.1 Reporting to FDA:

- Serious adverse events will be forwarded to FDA by the IND Office (Safety Project Manager IND Office) according to 21 CFR 312.32.

It is the responsibility of the PI and the research team to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the Merck's guidelines, and Institutional Review Board policy.

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.

Merck 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 Merck for human use.

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

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

Development of oral cancer is not considered an adverse event unless it is considered to be drug related by the investigator.

For the purpose of this study, adverse events that in the opinion of the treating investigator are related to planned procedures (e.g., usual pain, usual bleeding, intra- or post-procedure electrolyte imbalances and other clinically insignificant laboratory abnormalities) will not be captured and/or reported.

Adverse events will only be recorded for patients that undergo randomization. Adverse events will be recorded from the time the patient is randomized through the end of treatment / re-evaluation visit (month 3) or 90 days following cessation of treatment, whichever is longer.

Any new serious adverse event that occurs more than 30 days after last study drug administration should be reported if considered related to study drug (e.g., secondary cancer). Should a patient discontinue from or complete the study and commence subsequent anticancer therapy within 30 days of the last study drug administration, adverse events attributable to this subsequent therapy should not be recorded.

Laboratory abnormalities are usually not recorded as adverse events; however, signs and/or symptoms that are associated with laboratory findings requiring study withdrawal, dose modification, or medical intervention (e.g., anemia requiring transfusions or hyperglycemia requiring treatment) or other abnormal assessments (e.g., ECG, radiographs, vital signs) must be recorded as adverse events (or serious adverse events) if they meet the definition of an adverse event (or serious adverse event). In addition, laboratory abnormalities marked as clinically significant should also be recorded as adverse events. The investigator will report the most severe grade of the clinically significant laboratory abnormality and will evaluate its relationship to the study drug and clinical condition.

7.2.2 Definition of an Overdose for This Protocol

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

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

If a dose of Merck's product 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."

7.2.3 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be recorded in the trial database. Events of clinical interest for this trial include:

1. an overdose of Merck product, as defined in " Definition of an Overdose for This Protocol" that is not associated with clinical symptoms or abnormal laboratory results.

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

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

1. Additional adverse events:

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

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

7.2.4 Evaluating Adverse Events

An investigator who is a qualified physician will evaluate all adverse events according to the NCI Common Terminology for Adverse Events (CTCAE), version 4.0. Any adverse event

which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the adverse event. PDMS/CORe will be the electronic database used for this study.

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

7.3 Investigator Communications with Merck

All reports of overdose with and without an adverse event must be reported within 24 hours to the IND Office and within 2 working days hours to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220)

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), including the pregnancy of a male subject's female partner that occurs during treatment with pembrolizumab on the trial or within 120 days of completing pembrolizumb treatment on the trial, or 30 days following cessation of pembrolizumab treatment if the subject initiates new anticancer therapy, whichever is earlier. All subjects and female partners of male subjects who become pregnant must be followed to the completion/termination of the pregnancy. The outcome of the pregnancy will be reported to the IND Office and to Merck Global Safety (Attn: Worldwide Product Safety; FAX 215 993-1220) without delay, and within 24 hours to the IND Office and within 2 working days to Merck. 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),

it must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

7.3.1. Immediate Reporting Serious Adverse Events to Merck

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

- Results in death;
- Is life threatening;
- Results in persistent or significant disability/incapacity;
- Results in or prolongs an existing inpatient hospitalization;
- Is a congenital anomaly/birth defect;
- Is a new cancer (that is not a condition of the study);
- Is associated with an overdose;
- Is another important medical event

Refer to Table 6 for additional details regarding each of the above criteria.

Any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study that occurs to any subject from the time the subject is randomized through 90 days following cessation of treatment, or the initiation of new anti-cancer therapy, whichever is earlier, whether or not related to Merck product, must be reported within 5 working days of knowledge of the event to the IND Office and within 2 working days to Merck Global Safety.

ECIs (both non-serious and serious adverse events) identified in this guidance document from the date of first dose through 90 days following cessation of treatment, or 30 days after the initiation of a new anticancer therapy, whichever is earlier, need to be reported within 24 hours to the IND Office and within 2 working days to Merck Global Safety(Attn: Worldwide Product Safety; FAX 215 993-1220), regardless of attribution to study treatment, consistent with standard SAE reporting guidelines.

Non-serious Events of Clinical Interest will be forwarded to Merck Global Safety and will be handled in the same manner as SAEs.

Additionally, any serious adverse event, considered by an investigator who is a qualified physician to be related to Merck product that is brought to the attention of the investigator at any time outside of the time period specified in the previous paragraph also must be reported immediately to the IND Office and to Merck.

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

Table 6 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 Merck 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 [including hospitalization for an elective procedure] for a preexisting condition which has not worsened does not constitute a serious adverse event.); 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 oral cancer) **or**	
	Is an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours.	
	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	
Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the adverse event cause the Merck product to be discontinued?	
Relationship to test drug	Did the Merck product cause the adverse event? The determination of the likelihood that the Merck 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 Merck product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Merck product caused the adverse event (AE):	
	Exposure	Is there evidence that the subject was actually exposed to the Merck 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 Merck 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 Merck product (continued)	**The following components are to be used to assess the relationship between the test drug and the AE: (continued)**	
	Dechallenge	Was the Merck 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 Merck product; or (3) the trial is a single-dose drug trial); or (4) Merck product(s) is/are only used one time.)
	Rechallenge	Was the subject re-exposed to the Merck 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) Merck 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 MERCK PRODUCT, OR IF REEXPOSURE TO THE MERCK PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE SUBJECT, THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE Principle Investigator 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 Merck product or drug class pharmacology or toxicology?
The assessment of relationship will be reported on the ~~case report forms /worksheets~~ trial database 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 Merck product relationship).**	
Yes, there is a reasonable possibility of Merck product relationship.	There is evidence of exposure to the Merck product. The temporal sequence of the AE onset relative to the administration of the Merck product is reasonable. The AE is more likely explained by the Merck product than by another cause.	
No, there is not a reasonable possibility Merck product relationship	Subject did not receive the Merck product OR temporal sequence of the AE onset relative to administration of the Merck product is not reasonable OR there is another obvious cause of the AE. (Also entered for a subject with overdose without an associated AE.)	

8.1 STATISTICAL CONSIDERATIONS

8.2 Study design and sample size justifications

This randomized phase 2 trial focuses on the definitive primary endpoint of oral cancer-free survival, thus eliminating the limitations of utilizing intermediate endpoints for efficacy analysis. Unfortunately, clinical and/or histologic responses of IEN lesions to chemoprevention interventions only marginally correlate with long-term oral cancer-free survival, as demonstrated by larger-scale retinoid-based therapy trials.[13] As such, the most appropriate way to accurately estimate activity of a candidate drug to manage oral IEN is to use oral cancer-free survival as an endpoint.

The advantages of selecting a molecularly-defined high risk group as the eligible population include: (1) increased number of expected events, thus reducing the sample size; (2) avoidance of exposure of low-risk individuals to the drug, who are unlikely to develop oral cancer and therefore, unlikely to benefit from prevention interventions; (3) improvement of benefit/risk rations and benefit/cost ratios, justifying further use of the drug if positive effects are identified.

The proposed study will be an open-label, observation-controlled randomized study to evaluate the effect of pembrolizumab in a high-risk group of oral IEN patients. There will be two categories of high-risk patients in this study: (a) loss of heterozygosity (LOH) at 3p14 and/or 9p21 in the oral IEN of patients with a history of curatively treated oral cancer and (b) LOH at 3p14 and/or 9p21 plus at one other chromosomal region in the IEN of patients with no oral cancer history.

Study Duration: The trial period is 7 years with 4 years of accrual and 3 additional years of follow-up after last patient's enrollment.

Study Endpoints: The primary endpoint is oral cancer-free survival in patients receiving pembrolizumab as compared with the observation group. Multiple secondary and/or exploratory endpoints will be assessed as outlined in Section 3.2 and 3.3.

Treatment Groups: This is a 2-arm open-label Phase II single-center trial of pembrolizumab versus observation in patients with oral IEN. The trial will randomize 104 patients (1:1)to receive pembrolizumab versus observation.

Sample Size Justification

The planned sample size is 104 patients. In the recently completed EPOC study, 5.7 patients per month were screened for LOH high risk profiles, 68% were LOH positive, and 59% of the LOH positive patients agreed to be randomized.[11] That study had similar eligibility criteria as proposed herein. As such, we anticipate that for this trial, 250 patients will be screened over 4 years to achieve a total of 104 patients randomized. Sample size calculation was made on the basis of the primary endpoint of the study, time from randomization to onset of oral cancer or death.

Details of the assumptions used for the sample size calculation are listed below.

1. The study has a 4-year period to accrue 56 oral IEN/prior cancer and 48 IEN-alone patients, with an additional 3 years of follow-up after last patient is enrolled. The total study duration is 7 years.

2. The anticipated yield of LOH screening (described earlier) will be approximately 68%. Assuming an accrual rate of 59% eligible patients, we will need to screen a total of 250 oral IEN patients in order to reach our total accrual goal.

3. Time-to-oral cancer development follows an exponential distribution. Based on the data described earlier, 21% of the patients with IEN/LOH associated with curatively treated oral cancer will develop oral cancer in two years, and 15% of the IEN/LOH-alone patients will develop oral cancer in two years.

4. Pembrolizumab, the active treatment, can reduce the 2-year oral cancer rate by 52% for the IEN/LOH-cancer history group, i.e., 2-year cancer rate will be reduced from 21% to 10%. This corresponds to a hazard ratio of 0.45. We assume the same treatment effect (hazard ratio) in the IEN/LOH-alone group, corresponding to the 2-year oral cancer rate reduction from 15% to 7%. The parameters, lambda, for the exponential distributions are 0.1179 (control) and 0.053 (treatment) in IEN/LOH-cancer history patients and 0.0813 (control) and 0.0366 (treatment) in IEN/LOH-alone patients, respectively.

5. We assume the rate of lost-to-follow up, which includes patient refusal, early drop out, or competing risk, etc. is 10%. The distribution of the time to loss to follow-up is assumed to be uniform.

6. Stratified log-rank test is used to compare the cancer-free survival between the active and control groups.

7. One interim analysis is planned at the end of year 3. The final analysis will be performed at the end of the study (year 7). We will apply the group sequential design with the O'Brien-Fleming boundary to control the overall one-sided type I error rate to 10%. The stopping boundaries, i.e. Standardized Z Scale, are 1.899 at the interim analysis and 1.343 at the final analysis

Based on the above assumptions, we ran simulation studies with 10,000 replications. The results show that a total of 104 patients will allow us to have 79% power with a one-sided 10% type I error rate. The study will have 88% power to detect a hazard ratio of 0.4.

8.3 Statistical Analysis Plan

Patients' demographic and clinical characteristics at baseline will be summarized using descriptive statistics such as frequency distribution, mean (± s.d.) and median (range) accompanied by graphical analysis. Student t-test/Wilcoxon test and ANOVA/Kruskal-Wallis test will be used to compare continuous variables between different treatment groups. The chi-square test or the Fisher's exact test will be applied to assess the association between two categorical variables.

A CONSORT diagram will be used to summarize the conduct of the trial.[17]

The primary endpoint of the study is oral cancer-free survival defined as time from randomization to the development of histologically confirmed oral cancer or death of any cause, whichever occurs first. For events that have not occurred by the time of data analysis, times will be censored at the last contact at which the patient was known to be oral cancer-free. All patients will be analyzed on an intent-to-treat basis (i.e., as randomized). The distribution of time to oral cancer development will be estimated by the Kaplan-Meier method. Stratified log-rank test[18] will be used to compare cancer-free survival between treatment groups. The Cox (proportional hazards) regression model will be used to incorporate potential prognostic factors and treatment assignment as covariates.

In general, for both the primary endpoint and secondary endpoints, exploratory data analysis and graphical methods will be applied as the first step to examine the distribution of the data, error checking, and outlier identification. Range check and consistency check will be applied to ensure the data quality. Standard distribution plots such as the histogram and box-plot will be applied. A more versatile BLiP plot will be used to facilitate the plotting of both discrete and continuous data.[19] Event charts will be generated to study the relationship between multiple outcomes for time-to-event data at the individual level.[20] Descriptive statistics will be provided to summarize the data. Standard statistical methods for analyzing continuous data, discrete data, and survival data will be applied whenever appropriate.

Toxicity data will be summarized by frequency tables. For the efficacy endpoint, intend-to-treat analysis will be applied to the eligible patients. For the toxicity endpoint, per-treated analysis will be used to include any patient who received the treatment regardless of the eligibility nor the duration or dose of the treatment received.

9.1 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.2 Investigational Product

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

Clinical Supplies will be provided by Merck as summarized in Table 7.

Table 7 Product Descriptions

Product Name & Potency	Dosage Form
Pembrolizumab 50 mg	Lyophilized Powder for Injection
Pembrolizumab 100 mg/ 4mL	Solution for Injection

9.3 Packaging and Labeling Information

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

9.4 Clinical Supplies Disclosure

This trial is open-label; therefore, the subject, the trial site personnel, the IND Office and/or designee are not blinded to treatment. Drug identity (name, strength) is included in the label text; random code/disclosure envelopes or lists are not provided.

9.5 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.

9.6 Returns and Reconciliation

The investigator is responsible for keeping accurate records of the clinical supplies received from Merck or designee.

Upon completion or termination of the study, all unused and/or partially used investigational product will be destroyed at the site per institutional policy. It is the Investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

10.1 APPENDICES

10.2 ECOG Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.
* As published in Am. J. Clin. Oncol.: *Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.* The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.	

10.3 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)

10.4 Criteria for evaluating clinical and histologic responses

Definitions of clinical response (to be recorded at months 3 and 12):

- disease progression: increase of at least 25% in the sum of the product of the diameters of all visible lesions compared to baseline, and/or development of new lesions compared to baseline
- partial response: decrease of at least 50% in the sum of the product of the diameters of all visible lesions compared to baseline
- complete response: resolution of all baseline visible lesions
- stable disease: all other cases

Definitions of histological response (to be recorded at months 3 and 12):

- yes: resolution of baseline hyperplasia / hyperkeratosis / parakeratosis, resolution of baseline dysplasia, or improvement of baseline dysplasia by at least one grade
- no: all other cases

10.5 Events of Clinical Interest Guidance Document

Please refer to separate manual provided for biospecimen collection and handling.

10.6 Biospecimen Collection and Handling Guidelines

Please refer to separate manual provided for biospecimen collection and handling.

10.7 Pharmacy Manual

Please refer to separate manual provided for biospecimen collection and handling.

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