Clinical Trial Protocol and Statistical Plan

Title: Study of anti-PD1 Therapy for HPV-associated Recurrent Respiratory Papilloma Patients with Laryngeal, Tracheal and/or Pulmonary Involvement

DF/HCC Protocol ID# 15-469
NCT02632344
v.09282020

DF/HCC Protocol #: 15-469

Protocol Date: **September 28, 2020**

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1.0 TRIAL SUMMARY

Abbreviated Title	Phase II Study of pembrolizumab in Subjects with Human Papillomavirus-associated Recurrent Respiratory Papillomatosis
Trial Phase	II
Clinical Indication	The treatment of subjects with recurrent respiratory papillomatosis with extensive laryngeal, tracheal and/or pulmonary involvement
Trial Type	Interventional
Type of control	No treatment control
Route of administration	Intravenous
Trial Blinding	Unblinded Open-label
Treatment Groups	Pembrolizumab 200 mg every 3 weeks
Number of trial subjects	Approximately 22 subjects will be enrolled
Estimated enrollment period	Approximately 18-24 months
Estimated duration of trial	It is estimated that the trial will require approximately 60 months from the time the first subject signs the informed consent until the last subject's last visit.
Duration of Participation	Each subject will participate in the trial from the time the subject signs the Informed Consent Form (ICF) through the final protocol-specified contact. After a screening phase of 28 days, eligible subjects will register then to receive treatment on Day 1 of each 3-week dosing cycle. Treatment with pembrolizumab will continue until documented confirmed disease progression, unacceptable adverse event(s), intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw the subject, subject withdraws consent, pregnancy of the subject, noncompliance with trial treatment or procedure requirements, completion of 24 months of treatment with pembrolizumab, or administrative reasons. Subjects who attain a complete response may consider stopping trial treatment if they meet criteria for holding therapy. These subjects will be eligible for re-treatment after experiencing disease progression at the discretion of the investigator if they meet the criteria for re-treatment and the trial is ongoing. After the end of treatment, each subject will be followed for 30 days for adverse event monitoring (serious adverse events will be collected for 90 days after the end of treatment). Subjects who discontinue protocol treatment for reasons other than disease progression will have post-treatment follow-up for disease status until first disease progression, initiating a non-study cancer treatment, withdrawing consent, becoming lost to follow-up, death, or 36 months from study registration whichever occurs first. Following first disease progression, subjects will be followed by telephone for overall survival until death, withdrawal of consent, or 36 months from study registration whichever occurs first.

2.0 TRIAL DESIGN

2.1 Trial design

This is a non-randomized phase II trial in male and female subjects diagnosed with recurrent respiratory papillomatosis (RRP) with extensive laryngeal, tracheal and/or pulmonary involvement. Approximately 22 subjects will be enrolled in this trial to examine the safety and efficacy in this subject population who would be administered up to 200 mg of pembrolizumab every 3 weeks. Subjects will be evaluated every 3 weeks (21 days +/- 3 days) in the clinic with a video-recorded transnasal flexible laryngoscopy and tracheoscopy examination to assess clinical response on treatment (**Appendix A**) as well as evaluated every 24 weeks (169 days $\pm$ 14 days) with CT scans to assess response per volumetric analysis. For those patients with pulmonary lesions measurable by RECIST 1.1, CT scans of the chest will be obtained every 12 weeks (84 days +/- 7 days) to assess response per RECIST 1.1 criteria. In addition, patients will complete quality of life questionnaires to assess preference of pembrolizumab as compared to standard of care treatment, which is surgery, for this patient population (**Appendix F**).

As part of the natural course of this disease, patients undergo operative procedures for repeated debridement of papillomata within their upper aerodigestive tract in order to improve their breathing and/or voice quality. Prior to starting pembrolizumab, subjects will undergo a comprehensive laryngoscopy and tracheobronchoscopy to map and score their disease burden in the upper aerodigestive tract and a pre-treatment biopsy would be obtained at that time. Subsequently, at a minimum of every 12 weeks (84 days $\pm$ 14 days), subjects will be taken to the operating room for a comprehensive laryngoscopy and tracheobronchoscopy and debridement of any papillomatous lesions which obstructs the caliber of their airway by more than 50% and/or other lesions at the discretion of the surgeon. Some patients will require more frequent visits to the operating room depending on their disease burden and associated clinical symptoms. Biopsies will be obtained during all operative visits.

Adverse events will be monitored throughout the trial and graded in severity according to the guidelines outlined in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Treatment with pembrolizumab will continue until documented disease progression, unacceptable adverse event(s), intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw the subject, subject withdraws consent, pregnancy of the subject, noncompliance with trial treatment or procedure requirements, completion of 24 months of treatment with pembrolizumab, or administrative reasons. Subjects who attain an investigator-determined confirmed complete response (CR) may consider stopping trial treatment after receiving at least 24 weeks of treatment. Subjects who discontinue after at least 24 months of therapy for reasons other than disease progression or intolerability or who discontinue after attaining a CR may be eligible for up to one year of re-treatment after they have experienced clinical and/or radiographic disease progression. The decision to retreat will be at the discretion of the investigator if no additional systemic immunotherapeutic treatment was administered since the last dose of pembrolizumab, the subject still meets the safety parameters listed in the Inclusion/Exclusion criteria and the trial remains open.

After the end of treatment, each subject will be followed for 30 days for adverse event monitoring (serious adverse events will be collected for 90 days after the end of treatment). Subjects who discontinue treatment for reasons other than first disease progression will have post-treatment follow-up for disease status until disease progression, initiating a non-study systemic chemotherapeutic treatment, withdrawing consent, becoming lost to follow-up, death, or 36 months post study registration whichever occurs first. Following first disease progression, subjects will be followed by telephone contact for overall survival until death, withdrawal of consent or 36 months post study registration, whichever comes first. The study will be stopped if greater than 30% of patients discontinue pembrolizumab due to an adverse event or for any patient death related to toxicity.

The goal of this study is to evaluate the efficacy of pembrolizumab in this patient population to support treatment with systemic immunotherapy which could minimize and/or eliminate the need for multiple surgical procedures over the patient's lifetime. The primary objectives of the trial are to determine the anti-tumor activity, safety, and tolerability of pembrolizumab treatment in male and female subjects diagnosed with RRP. Secondary objectives include evaluating the relationship between candidate efficacy/resistance biomarkers and anti-tumor activity and response duration of pembrolizumab. An exploratory objective is to assess the quality of life of RRP patients with pembrolizumab. Established quality of life is lacking in this patient population and, in a separate study, we are establishing baseline quality of life parameters of RRP patients being treated with standard of care, which is repeated surgeries.

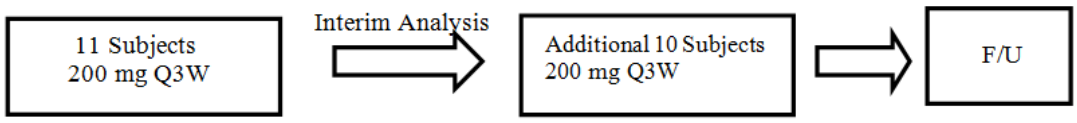
The study will be conducted in conformance with Good Clinical Practices.

Specific procedures to be performed during the trial, as well as their prescribed times and associated visit windows, are outlined in the Trial Flow Chart – Section 9.0. Details of each procedure are provided in Section 10.0 – Trial Procedures.

2.2 Trial Diagram

The trial design is depicted in Figure 1.

Figure 1. Trial Design



3.0 OBJECTIVES & HYPOTHESES

3.1 Primary Objectives & Hypotheses

(1) **Objective:** To determine the best overall clinical response rate (ORR: CR+PR) in subjects with RRP with extensive laryngeal, tracheal and/or pulmonary involvement based on clinical examination and/or RECIST 1.1.

Hypothesis: Intravenous administration of pembrolizumab to subjects with RRP will result in a clinically meaningful overall response rate based on clinical examination and/or RECIST 1.1.

(2) **Objective:** To determine the safety and tolerability of pembrolizumab in subjects with RRP.

Hypothesis: Intravenous administration of single agent pembrolizumab is sufficiently well-tolerated to permit continued clinical investigation.

3.2 Secondary Objectives & Hypotheses

(1) **Objective**: To evaluate changes in the expression of various immune biomarkers and investigate the relationship between candidate efficacy/resistance immune biomarkers and anti-tumor activity of pembrolizumab utilizing pre- and on-treatment tissue biopsies and blood sampling.

Hypothesis: Intravenous administration of single agent pembrolizumab will result in a clinically meaningful change in the tumor microenvironment.

(2) **Objective**: To evaluate the response duration in subjects receiving pembrolizumab.

Hypothesis: Intravenous administration of single agent pembrolizumab will result in a clinical meaningful response which will lengthen the time interval between required surgical debridements.

3.3 Exploratory Objective & Hypothesis

(1) **Objective:** To assess the quality of life (QOL) with immunotherapy treatment as compared to standard of care treatment in RRP patients.

Hypothesis: Treatment with intravenous administration of pembrolizumab improves the quality of life of RRP patients as compared to standard of care treatment, which is repeated surgical debridement over their lifetime.

4.0 BACKGROUND & RATIONALE

4.1 Background

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

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 Stated 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

This is a nonrandomized, phase II trial in male and female subjects diagnosed with RRP with extensive laryngeal, tracheal and/or pulmonary involvement.

Various mechanisms have been proposed for the resistance of human solid tumors to immune recognition and obliteration, including the recruitment of regulatory T cells (Tregs), myeloid derived suppressor cells (MDSC), and local secretion of inhibitory cytokines. Recent evidence that tumors co-opt physiologic mechanisms of tissue protection from inflammatory destruction through the upregulation of immune inhibitory ligands has provided a new perspective for understanding tumor immune resistance. Antigen-induced activation and proliferation of T cells are regulated by the temporal expression of both co-stimulatory and co-inhibitory receptors and their cognate ligands. Coordinated signaling through these receptors modulates the initiation, amplification, and subsequent resolution of adaptive immune responses. In the absence of co-inhibitory signaling, persistent T cell activation can lead to excessive tissue damage in the setting of infection as well as autoimmunity. However, in the context of cancer, in which immune responses are directed against antigens specifically or selectively expressed by tumor cells, immune checkpoints can represent major obstacles to the generation of clinically meaningful anti-tumor immunity. Therefore, efforts have been made in the clinical arena to investigate blockade of immune checkpoints as novel therapeutic approaches to cancer.

Our group recently found that the PD-1:PD-L1 immune checkpoint pathway facilitates persistent human papillomavirus (HPV) infection and subsequent development of HPV-associated head and neck squamous cell carcinomas (HPV-HNSCC) [1]. Our findings supported a model in which the PD-1:PD-L1 immune checkpoint pathway becomes induced as an adaptive resistance mechanism of tumor against host. Our study provided the rationale for therapeutic blockade of this pathway in patients with HPV-HNSCC.

Given the similar viral etiology, activation of the PD-1:PD-L1 pathway has also been evaluated in Recurrent Respiratory Papillomatosis (RRP) patients. A recent report documented that PD-1 was expressed on a very high percentage of CD4+ T cells and that respiratory papillomas contain

high levels of PD-L1 mRNA [2]. Independently, our group also has demonstrated positive staining for CD4, CD8, PD-1, and PD-L1 in RRP tissue as well as has been able to perform multi-color flow cytometry on RRP tissue to demonstrate enriched co-expression of PD-1 and other co-inhibitory T cell markers on tumor infiltrating lymphocytes (TILs).

RRP is caused by infection with the low-risk HPV types 6 and 11 and is the most common benign tumor of the airway that affects children and adults [3]. The virus induces the proliferation of benign squamous epithelium, most commonly in the larynx, which can have profound functional consequences for breathing and speech and result in a chronic, debilitating disease in the pediatric and adult populations [4]. The virus can also spread to the trachea and lungs and, subsequently, block the breathing passages in the lungs causing pulmonary collapse. Furthermore, given their chronic viral infection, the lesions are at increased risk for malignant transformation. Currently, there is no medical cure for RRP. Treatment generally involves repeated surgical debulking of the virally-infected cells, with an aim of increasing the airway caliber to help individuals breathe better and/or improve their voice. Some patients undergo hundreds of operative interventions over their lifetime to maintain their airway patency, and the risk of permanent hoarseness and vocal cord scarring increases with each operative intervention [5]. If left untreated, this disease can be a life-threatening situation leading to complications associated with lung collapse, suffocation, malignant transformation, and death [6]. Yet, with intervention, studies demonstrate that the impact on voice quality has the biggest impact on long-term quality of life for patients with RRP [7] and permanent vocal cord scarring can lead to life-long communication disorders and social stigmas. Thus, there is a strong unmet clinical need to develop novel therapies for RRP.

The clinical entity of RRP is defined by the multiple local recurrences of disease resulting from a tolerized host immune response to the virus; as there is no good systemic treatment option currently available for this "benign" disease, repeated surgical debridement remains the mainstay of therapy. Radiation and chemotherapy do not play a role in the management of this disease so these patients are naïve to these modalities. Infected subjects develop immunologic responses against the virus yet the T cells are anergized through activation of the PD-1:PD-L1 pathway. Therefore, there is a strong rationale to evaluate systemic immunomodulatory agents, such as anti-PD-1 therapy, in RRP patients and, given that the disease localizes to the mucosal lining of the upper aerodigestive tract, there is a window of opportunity which allows for directly visualizing clinical response during treatment.

4.2.2 Rationale for Dose Selection/Regimen/Modification

An open-label Phase I trial (Protocol 001) is being conducted to evaluate the safety and clinical activity of single agent pembrolizumab. The dose escalation portion of this trial evaluated three dose levels, 1 mg/kg, 3 mg/kg, and 10 mg/kg, administered every 2 weeks (Q2W) in subjects with advanced solid tumors. All three dose levels were well tolerated and no dose-limiting toxicities were observed. This first in human study of pembrolizumab 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 to date. Recent data from other clinical studies within the pembrolizumab program has shown that a lower dose of pembrolizumab and a less frequent schedule may be sufficient for target engagement and clinical activity.

PK data analysis of pembrolizumab administered Q2W and Q3W showed slow systemic clearance, limited volume of distribution, and a long half-life (refer to IB). Pharmacodynamic data (IL-2 release assay) suggested that peripheral target engagement is durable (>21 days). This early PK and pharmacodynamic data provides scientific rationale for testing a 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 pembrolizumab 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. Pembrolizumab 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 pembrolizumab 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 2 mg/kg and comparable doses of pembrolizumab in solid tumors is based on: 1) similar efficacy and safety of pembrolizumab when dosed at either 2 mg/kg or 10 mg/kg Q3W in melanoma patients, 2) the flat exposure-response relationships of pembrolizumab for both efficacy and safety in the dose ranges of 2 mg/kg Q3W to 10 mg/kg Q3W, 3) the lack of effect of tumor burden or indication on distribution behavior of pembrolizumab (as assessed by the population PK model) and 4) the assumption that the dynamics of pembrolizumab target engagement will not vary meaningfully with tumor type.

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

A fixed dose regimen will simplify the dosing regimen to be more convenient for physicians and to reduce potential for dosing errors. A fixed dosing scheme will also reduce complexity in the logistical chain at treatment facilities and reduce wastage. However, for the pediatric population, a dose based on weight (2 mg/kg up to a maximum of 200 mg) will be implemented.

4.2.3 Rationale for Endpoints

4.2.3.1 Efficacy Endpoints

The primary efficacy objective of this study is to evaluate the anti-tumor activity of pembrolizumab in male and female subjects diagnosed with RRP with extensive laryngeal, tracheal and/or pulmonary involvement. Response rate per clinical assessment and/or RECIST 1.1 will be evaluated in those subjects with disease measurable by RECIST.

Clinical response rates will be the primary measure for assessment of tumor response and as a basis for all protocol guidelines related to disease status (e.g. discontinuation of study therapy). Clinical response will be assessed by direct visualization and scoring of disease burden within the upper aerodigestive tract (**Appendix A: Surgical Scoring and Appendix G: CRFs**).

The burden of disease will be assessed at each direct laryngoscopy and tracheoscopy examination performed in the clinic and in the operating room, and the extent of papilloma growth will be measured using an instrument previously described [8, 9]. Briefly, evaluations will be made of five major anatomic sites in the larynx (epiglottis, false cords, ventricle, true cords, and subglottis), which are subdivided into 23 subsites. Four major anatomic sites in the tracheo-bronchial tree (trachea, tracheostomy site, if present, carina and mainstem bronchus) are divided into 6 subsites. The rating incorporates three components. Number of sites (AS) is the actual number of affected sites. For laryngeal disease, this value can range from 0 to 23. Surface area (SA) involvement at each major site is rated on the following scale: 0 (none), 1 (under 1/3 of area is affected), 2 (under 2/3 of area), or 3 (more than 2/3 of area). For the total of five major sites this value can range from 0 to 15. Extent of lumen obstruction (LO) reflects the degree of airway obstruction at each site, on a similar scale of 0-3. For the total of five major sites this value can range from 0 to 15. The three components (AS, SA and LO) are summed to yield a single overall rating, but the scores are entered separately into the computer to permit analysis of separate components of the score if desired. The potential range of this scoring system is 0 to 53 for laryngeal disease; the range observed in previous studies was 0 to 43 (www.clinicaltrials.gov; NCT00571701). Scores for tracheobronchial disease are calculated similarly. The maximum possible AS score is 6. The maximum SA and LO scores are each 12. Therefore, the maximum summed score for tracheo-bronchial involvement is 30. Copies of the scoring sheet pages are included in the appendix, as part of the case report forms.

Overall response rates according to clinical assessment will be derived from time-point response assessments as follows:

- **Complete Response (CR):** Complete disappearance of all tumor lesions (and no new lesions). CR must be confirmed by repeated, consecutive assessments made no less than 4 weeks from the date first documented.
- **Partial Response (PR):** Decrease in the summed score for laryngeal and tracheo-bronchial involvement by 25% or greater by a consecutive assessment at least 4 weeks after first documentation.
- **Stable Disease (SD):** Failure to meet criteria for CR or PR, in absence of PD.

- **Progressive Disease (PD):** At least 25% increase in the summed score for laryngeal and tracheo-bronchial involvement, confirmation by a repeat, consecutive assessment no less than 4 weeks from the date first documented.

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

For those patients with pulmonary lesions measurable by RECIST 1.1, CT scans of the chest will be obtained every 12 weeks (84 days +/- 7 days) to assess response per RECIST 1.1 criteria. Standard RECIST criteria may not provide a complete response assessment of immunotherapeutic agents such as pembrolizumab. Therefore, RECIST 1.1 will be used with the following adaptation:

If radiologic imaging shows PD, tumor assessment should be repeated a minimum of 4 weeks later in order to confirm PD with the option of continuing treatment per below while awaiting radiologic confirmation of progression. If repeat imaging shows a reduction in the tumor burden compared to the initial scan demonstrating PD, treatment may be continued as per treatment calendar. If repeat imaging confirms progressive disease, subjects will be discontinued from study therapy. In determining whether or not the tumor burden has increased or decreased, all target lesions as well as non-target lesions should be considered.

In subjects who have initial evidence of radiological PD, it is at the discretion of the treating physician whether to continue a subject on study treatment until repeat imaging is obtained a minimum of 4 weeks later. This decision should be based on the clinical judgment of the subject's overall clinical condition, including performance status, clinical symptoms, and laboratory data. Subjects may receive treatment while waiting for confirmation of PD if they are clinically stable as defined by the following criteria:

*absence of signs and symptoms indicating disease progression

*no decline in ECOG performance status

*absence of rapid progression of disease

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

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

Male and female subjects with RRP with tracheal and/or pulmonary involvement.

5.1.2 Subject Inclusion Criteria

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

1. The subject or their legal guardian be willing and able to provide written informed consent for the trial.

2. Be ≥ 18 years of age on day of signing informed consent and ≥ 12 years of age on day of signing assent.

3. Have histologically confirmed diagnosis of RRP that involves the trachea, lungs, and/or larynx. If a subject is enrolled with laryngeal disease only, the subject must have undergone at least 3 or more surgeries/procedures in any one year to remove the lesions from their larynx. Subjects must have evaluable disease either based on RECIST 1.1 and/or endoscopic parameters, as discussed above.

4. Be required to provide tissue from a newly obtained biopsy of a tumor lesion. *Newly-obtained is defined as a specimen obtained up to 6 weeks (42 days) prior to study registration. Subjects for whom newly-obtained samples cannot be provided (e.g. inaccessible or subject safety concern) may submit an archived specimen only upon agreement from PI.*

5. Have confirmed human papillomavirus-associated lesions based on in-situ hybridization testing and/or polymerase chain reaction which may be performed on a newly obtained biopsy or archived sample.

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

7. Demonstrate adequate organ function as defined in Table 1, all screening labs should be performed within 28 days of study registration.

Table 1: Adequate Organ Function Laboratory Values

SYSTEM	LABORATORY VALUE
Hematological	
Absolute neutrophil count (ANC)	≥1,500 /mcL
Platelets	≥100,000 / mcL
Hemoglobin	≥9 g/dL or ≥5.6 mmol/L without transfusion or EPO dependency (within 7 days of assessment)
Renal	
Serum creatinine **OR** Measured or calculated[a] creatinine	≤1.5 X institutional upper limit of normal (ULN) **OR**

SYSTEM	LABORATORY VALUE
clearance (GFR can also be used in place of creatinine or CrCl)	≥60 mL/min for subject with creatinine levels > 1.5 X institutional ULN
Hepatic	
Serum total bilirubin	≤ 1.5 X institutional ULN **OR**
	Direct bilirubin ≤ institutional ULN for subjects with total bilirubin levels > 1.5 institutional ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 X institutional ULN **OR** ≤ 5 X institutional ULN for subjects with liver metastases
Albumin	≥2.5 mg/dL
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT) Activated Partial Thromboplastin Time (aPTT)	≤1.5 X institutional ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants ≤1.5 X institutional ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
[a]Creatinine clearance should be calculated per institutional standard.	

8. Female subject of childbearing potential should have a negative urine or serum pregnancy test within 28 days of study registration*. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. *Please refer to the study calendar for requirements regarding a pregnancy test 72 hours prior to receiving any dose of study medication upon subject enrollment into the study.

9. Female subjects of childbearing potential should be willing to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study medication (Reference Section 7.6.2). Subjects of childbearing potential are those who have not been surgically sterilized or have not been free from menses for > 1 year. The methods of surgical sterilization include having had a hysterectomy (removal of the uterus), bilateral oophorectomy (removal of both ovaries), tubal ligation (having your tubes tied), and transvaginal occlusion (blocking the tubes with a coil).

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

5.1.3 Subject Exclusion Criteria

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

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

2. Has a known diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to study registration.

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

4. Has a known hypersensitivity to pembrolizumab or any of its excipients.

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

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

7. Recovery from effects of any major surgery or significant traumatic injury at least 28 days before the first dose of study treatment. Endoscopic debridement of RRP lesions is NOT considered a major surgery

8. Has a known diagnosis of invasive squamous cell carcinoma within the past 2 years.

9. Patients with invasive squamous cell carcinoma derived from their RRP who are not considered appropriate for surgery, radiation therapy, or chemotherapy by their treating oncology team may be considered eligible for the study.

10. 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.

11. Has a history of (non-infectious) pneumonitis that required steroids or current pneumonitis.

12. Evidence of interstitial lung disease.

13. Has an active infection requiring systemic therapy.

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

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

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

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

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

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

20. 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.*

6.0 REGISTRATION PROCEDURES

6.1 GENERAL GUIDELINES FOR DF/HCC INSTITUTIONS

Institutions will register eligible participants in the Clinical Trials Management System (CTMS) OnCore. Registrations must occur prior to the initiation of protocol therapy. Any participant not registered to the protocol before protocol therapy begins will be considered ineligible and registration will be denied.

An investigator will confirm eligibility criteria and a member of the study team will complete the protocol-specific eligibility checklist.

Following registration, participants may begin protocol therapy. Issues that would cause treatment delays should be discussed with the Overall Principal Investigator (PI). If a participant does not receive protocol therapy following registration, the participant's registration on the study must be canceled. Registration cancellations must be made in OnCore as soon as possible.

Registration Process for DF/HCC Institutions

DF/HCC Standard Operating Procedure for Human Subject Research Titled *Subject Protocol Registration* (SOP #: REGIST-101) must be followed.

General Guidelines for Other Investigative Sites

Eligible participants will be entered on study centrally by the Coordinating Center. All sites should call the Coordinating Center to verify slot availabilities.

Following registration, participants should begin protocol treatment within 14 days of registration. Issues that would cause treatment delays should be discussed with the Principal Investigator/Sponsor. If a participant does not receive protocol therapy following registration, the participant's registration on the study must be canceled. The Coordinating Center should be notified of cancellations as soon as possible

Registration Process for Other Investigative Sites

To register a subject, the following documents should be completed by the participating institution and forwarded to the Coordinating Center:

- Copy of source documentation for inclusion/exclusion criteria and screening procedures, including but not limited to
  - Pathology report
  - Medical history and physical exam
  - Laboratory reports
  - Concomitant medication list
- Demographics information.
- Signed study consent form.
- Study Entry Note
- HIPAA authorization form, if applicable
- Eligibility checklist

The Coordinating Center will review the above documentation to confirm eligibility and consent. To complete the registration process, the Coordinating Center will follow DF/HCC Standard Operating Procedure for Human Subject Research Titled *Subject Protocol Registration* (SOP #: REGIST-101) and register the participant on the protocol. Once registered a confirmation email with the participant study number, and if applicable the dose treatment level, will be sent to the participating site.

NOTE: Registrations can only be conducted by the Coordinating Center during the business hours of 8:30 AM and 5:00 PM Eastern Standard Time (or Eastern Daylight Time when applicable), Monday through Friday. A complete registration packet, including all documents listed above, must be received at least 1 business day *prior to* the anticipated registration to ensure adequate review. Same day treatment registrations will only be accepted with prior notice and discussion with the DF/HCC Lead Institution.

Treatment may not begin without confirmation from the Coordinating Center that the participant has been registered.

7.0 TREATMENT PLAN

7.1 Treatment Regimen

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

Table 2: Trial Treatment

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

* For the pediatric population, the dose is 2 mg/kg up to a maximum of 200 mg

7.1.1 Dose Selection/Modification

7.1.1.1 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 are provided in the Pharmacy Manual.

7.1.1.2 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 7.5.1 and Events of Clinical Interest (ECI) Guidance Document (Appendix E) 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 Hyperglycemia	T1DM or 3-4	Hold pembrolizumab for new onset Type 1 diabetes mellitus or Grade 3-4 hyperglycemia associated with evidence of beta cell failure.	Resume pembrolizumab when patients are clinically and metabolically stable.
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

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Discontinue Subject
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 3 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the patient's study record.

7.1.2 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 9.0). Trial treatment may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative or other reasons.

All trial treatments will typically be administered on an outpatient basis.

Pembrolizumab up to 200 mg will be administered as a 30 minute IV infusion every 3 weeks. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min). Pembrolizumab will be administered after the operative endoscopy. If the patient is found to have progressive disease by endoscopic evaluation, the patient will continue to receive pembrolizumab until the next in–office clinical examination in 3 weeks which confirms progressive disease of the target lesion.

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

7.1.3 Trial Blinding/Masking

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

7.1.4 Stopping Rules

The study will be stopped if greater than 30% of patients discontinue pembrolizumab due to an adverse event or for any patient death related to toxicity.

7.2 Randomization or Treatment Allocation

Subjects participating in this trial will be allocated to trial treatment by non-random assignment.

7.3 Stratification

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

7.4 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 investigator should discuss any questions regarding this with the Merck Clinical team. The final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary physician.

7.4.1 Acceptable Concomitant Medications

All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the case report form (CRF) including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF.

All concomitant medications received within 28 days prior to study registration and 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered after 30 days after the last dose of trial treatment should be recorded for SAEs and ECIs as defined in Section 11.0: Adverse Event Reporting Requirement.

7.4.2 Prohibited Concomitant Medications

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

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab
- Radiation therapy
    - Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed at the investigator's discretion.
- 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 Sponsor.
- Intralesional or systemic antiviral treatment within 30 days prior to the first dose of trial treatment and while participating in the trial.

Subjects who, in the assessment by the treating investigator, require the use of any of the aforementioned treatments for clinical management should be removed from protocol treatment. Subjects may receive other medications that the treating 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.

7.5 Rescue Medications & Supportive Care

7.5.1 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 7.1.1 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 greater than 3 days, 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 3-4** 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 at least 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 intravenous 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
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). Subsequent rate of infusions should be no more than 50% of rate at which reaction occurred.
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.		

7.6 Diet/Activity/Other Considerations

7.6.1 Diet

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

7.6.2 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 start using birth control from study Visit 1 throughout the study period up to 120 days after the last dose of study therapy.

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

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study they must adhere to the contraception requirement (described above) for the duration of the study and during the follow-up period defined in Section 11.5.6: Reporting of Pregnancy and Lactation to the Sponsor 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.

7.6.3 Use in Pregnancy

If a subject inadvertently becomes pregnant while on treatment with pembrolizumab, the subject will immediately be removed from the study treatment. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the Coordinating Center and to Merck without delay; if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn), the outcome must be reported within 24 hours to the Coordinating Center and within 2 working days to Merck.

The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor. If a male subject impregnates his female partner the study personnel at the site must be informed immediately and

the pregnancy reported to the Coordinating Center and to Merck and followed as described above and in Section 11.5.6.

7.6.4 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.

7.7 Criteria for Removal from Protocol Treatment

Subjects may withdraw consent for protocol treatment and/or study itself at any time for any reason or be removed from the protocol treatment and/or study itself at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the treating investigator or the Sponsor if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding discontinuation or withdrawal are provided in Section 10.1.4: Other Procedures.

Treatment may continue until one of the following criteria applies:

- The subject withdraws consent to treatment.
- Confirmed radiographic disease progression

  ***NOTE**: A subject may be granted an exception to continue on treatment with confirmed radiographic progression if clinically stable or clinically improved*

- Unacceptable adverse experiences as described in Section 7.1.1
- Intercurrent illness that prevents further administration of treatment
- Investigator's decision to withdraw the subject
- The subject has a confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements
- The subject is lost to follow-up
- Completed 24 months of uninterrupted treatment with pembrolizumab or 35 administrations of study medication, whichever is later.

  ***NOTE**: 24 months of study medication is calculated from the date of first dose. Subjects who stop pembrolizumab after 24 months may be eligible for up to one year of additional study treatment if they progress after stopping study treatment provided they meet the requirements detailed in Section 10.1.5.5*

- Treatment was held for 9 weeks for reasons other than complete response
- Administrative reasons

Participants will be removed from the protocol therapy when any of these criteria apply. Participants removed from protocol therapy for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event. Alternative care options will be discussed with the participant.

The reason for removal from protocol therapy, and the date the participant was removed, must be documented in the case report form (CRF). The research team also updates the relevant Off Treatment/Off Study information in OnCore; the Coordinating Center updates the relevant information for participating sites.

The End of Treatment and Follow-up visit procedures are listed in Section 9 (Protocol Flow Chart) and Section 10.1.5 (Visit Requirements). After the end of treatment, each subject will be followed for 30 days for adverse event monitoring (serious adverse events will be collected for 90 days after the end of treatment). Subjects who discontinue for reasons other than first progressive disease will have post-treatment follow-up for disease status until disease progression, initiating a non-study cancer treatment, withdrawing consent, becoming lost to follow-up, death, or 36 months post-study registration. After documented first disease progression each subject will be followed by telephone for overall survival until death, withdrawal of consent, or 36 months post-study registration, whichever occurs first.

7.8 Discontinuation of Study Therapy after CR

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

7.9 Subject Replacement Strategy

Additional subjects may be enrolled to ensure that the required number of evaluable subjects in each cohort is achieved. A subject that discontinues protocol treatment for first progressive disease or a drug-related AE will not be replaced and will be counted in the evaluable population of subjects for the respective cohort.

7.10 Criteria for Removal from the Study

Participants will be removed from study when any of the following criteria apply:

- The subject or legal representative (such as a parent or legal guardian) withdraws consent.
- Death
- Investigator's decision to withdraw the subject

- Noncompliance with trial treatment or procedure requirements
- The subject is lost to follow-up
- Other administrative reasons

The reason for taking a participant off study, and the date the participant was removed, must be documented in the case report form (CRF).

The research team updates the relevant Off Treatment/Off Study information in OnCore; the Coordinating Center updates the relevant information for participating sites.

7.11 Clinical Criteria for Early Trial Termination

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

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

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

8.0 BIOMARKER, CORRELATIVE AND SPECIAL STUDIES

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

Assays may include but are not limited to:

Multi-parametric IHC
Spatial association of PD-1+ tumor infiltrating lymphocytes (TILs) and PD-L1+ cells (tumor and myeloid cells) suggests “induction” of PD-L1. Interferon-gamma (IFN-g) production by antigen-specific PD-1+ CD8+ T cells is hypothesized to drive local intratumoral upregulation of PD-L1 on adjacent tumor and myeloid cells, leading to a “stalled cytotoxic T cell (CTL)” response which may be predictive of response to pembrolizumab therapy. By assessing both the required elements and identifying the cell types which are expressing these proteins, a multi-color IHC assay may be a better predictor of response than PD-L1 positivity alone.

Transcriptional Analyses
Next-generation sequencing (RNAseq) will be used to profile global RNA expression in tissue specimens, to define a gene set critical for clinical response to pembrolizumab. The hypothesis to be tested is that pembrolizumab responders will exhibit a “stalled CTL” response within the

tumor reflected in the physical proximity between PD-1 and PD-L1 expression and the presence of an aborted interferon-gamma transcriptional program will be detectable by profiling analyses. Expression of individual genes related to the immune system may also be evaluated, such as immune signatures and critical cytokines (e.g., IL-10).

Gene Sequencing
New data are emerging that suggest we can define certain tumor types as being 'hypermutated' or expressing neoantigens. There is a potential that this hypermutated state may correlate with response to pembrolizumab therapy, and/or that the converse, 'hypomutated' state may correlate with non-response.

T cell receptor (TCR) repertoire
Tumor infiltrating lymphocytes will be extracted from the tissue and TCR diversity assessed with the treatment of Pembrolizumab.

8.1 Sample Instructions

8.1.1 Specimens Required

Correlative Blood Samples

Study Screening and D1 of each cycle corresponding to an operating room visit
- Ten 10ml green top or CPT tubes*
- One 10 ml red top

*For the pediatric population, five 10 ml green top or CPT tubes would be needed for study screening.

Blood sample tubes should be completely filled to ensure adequate sample for testing.

Tissue Samples

A fresh tissue biopsy will be collected and processed as a formalin fixed paraffin embedded tumor block and a separate piece stored in RNALater at 4oC, when sufficient tissue is present, at the baseline endoscopy and at each operating room visit.

Specimens must be collected on Mondays, Tuesdays, Wednesdays or Thursdays for same-day shipment.

Archival formalin fixed paraffin embedded tumor blocks and/or unstained slides will also be requested for the correlative assays stated in Section 8.0.

8.1.2 Processing Information

8.2 Shipping Instructions

The correlative blood samples and/or tissue should be shipped for overnight delivery to:

Sara Pai, MD, PhD
Massachusetts General Hospital
255 Charles St GRJ-910
Boston MA, 02114

Archival tissue can be batched shipped ambient to:

Sara Pai, MD, PhD
Massachusetts General Hospital
255 Charles St GRJ-910
Boston MA, 02114

Prior to shipping any samples, please email Dr. Pai (sara.pai@mgh.harvard.edu) and the Coordinating Center with confirmation of the shipment including an inventory of the samples included and a tracking number. Ship Monday, Tuesday, Wednesday, or Thursdays as shipments cannot be received on weekends and/or on holidays. The inventory sheet must accompany each shipment and include a complete list of samples shipped (patient number, time point, study #) and a contact name, address and phone number of the person who is responsible for the shipment. Please sign and date the inventory sheet and retain a copy for site record maintenance. .

8.2.1 Labeling Instructions

Each tube should be labeled as follows:

DFCI #: 15-469
Study of anti-PD1 Therapy for
HPV-associated RRP Patients
Subject ID:
Subject Initials:
Visit#: Date:

8.2.2 Storage and Shipping Instructions

The research related blood and tissue must be stored in a secure, limited-access location until shipment. The samples should be shipped Monday through Thursday for overnight delivery. Participating sites are responsible for packaging and shipping expenses.

9.0 TRIAL FLOW CHART

9.1 Study Flow Chart

Trial Period:	**Screening Phase**		**Treatment Cycles**								**End of Treatment (early or at 24 months)**	**Post-Treatment**		
							To be repeated beyond 8 cycles							
Treatment Cycle/Title:		Main Study Screening (Visit 1)	1	2	3	4	5	6	7	8	Discon	Safety Follow-up	Follow Up Visits[24]	Survival Follow-Up
Scheduling Window (Days)[1]:		-28 to -1		± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days post discon ± 2 weeks	Every 8 weeks post discon ± 2 weeks	Every 24 weeks ± 2 weeks
Administrative Procedures														
Informed Consent[2]		X												
Inclusion/Exclusion Criteria		X												
Demographics and Medical History		X												
Prior and Concomitant Medication Review[3]		X	X	X	X	X	X	X	X	X	X	X[3]		
Trial Treatment Administration			X	X	X	X	X	X	X	X				
Post-study anticancer therapy status													X	X[20]
Survival Status														X[20]
Clinical Procedures/Assessments														
Review Adverse Events[4]			X	X	X	X	X	X	X	X	X	X[5]	X[5]	
Full Physical Examination[6]		X					X							

Trial Period:	**Screening Phase**		**Treatment Cycles**								**End of Treatment (early or at 24 months)**	**Post-Treatment**		
							To be repeated beyond 8 cycles							
Treatment Cycle/Title:		Main Study Screening (Visit 1)	1	2	3	4	5	6	7	8	Discon	Safety Follow-up	Follow Up Visits[24]	Survival Follow-Up
Scheduling Window (Days)[1]:		-28 to -1		± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days post discon ± 2 weeks	Every 8 weeks post discon ± 2 weeks	Every 24 weeks ± 2 weeks
Directed Physical Examination[6]			X	X	X	X		X	X	X	X			
Vital Signs and Weight[7]		X	X	X	X	X	X	X	X	X	X			
ECOG Performance Status		X	X	X	X	X	X	X	X	X	X	X		
Laboratory Procedures/Assessments: analysis performed by LOCAL laboratory														
Pregnancy Test –Serum β-HCG[8]		X	X	X	X	X	X	X	X	X				
PT/INR and aPTT[9]		X[10]												
CBC with Differential[11]		X[10]	X	X	X	X	X	X	X	X	X	X[17]		
Comprehensive Serum Chemistry Panel[11]		X[10]	X	X	X	X	X	X	X	X	X	X[17]		
Urinalysis[11]		X[10]				X[12]					X	X[17]		
T3, FT4 and TSH[11]		X[10]				X[12]						X[17]		
Efficacy Measurements														
Radiographic Tumor Imaging[13]		X								X[14]	X[15]		X[16]	X[20]
Clinical Imaging: Video-recording of flexible fiberoptic laryngoscopy, tracheoscopy, and/or bronchoscopy examination[22]		X[21]	X	X	X	X	X	X	X	X	X[15]	X	X	X[20]
Tumor Biopsies/Archival Tissue Collection/Correlative Studies Blood														

Trial Period:	**Screening Phase**		**Treatment Cycles**								**End of Treatment (early or at 24 months)**	**Post-Treatment**		
							To be repeated beyond 8 cycles							
Treatment Cycle/Title:		Main Study Screening (Visit 1)	1	2	3	4	5	6	7	8	Discon	Safety Follow-up	Follow Up Visits[24]	Survival Follow-Up
Scheduling Window (Days)[1]:		-28 to -1		± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days post discon ± 2 weeks	Every 8 weeks post discon ± 2 weeks	Every 24 weeks ± 2 weeks
Archival or Newly Obtained Tissue Collection		X				X[18]				X[18]	X[19]			
HPV testing		X												
Correlative Studies Blood Collection		X				X				X	X[19]			
Quality of Life Questionnaires[23]		X				X				X	X[19]			

Trial Period:	**Screening Phase**		**Treatment Cycles**								**End of Treatment (early or at 24 months)**	**Post-Treatment**		
							To be repeated beyond 8 cycles							
Treatment Cycle/Title:		Main Study Screening (Visit 1)	1	2	3	4	5	6	7	8	Discon	Safety Follow-up	Follow Up Visits[24]	Survival Follow-Up
Scheduling Window (Days)[1]:		-28 to -1		± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days post discon ± 2 weeks	Every 8 weeks post discon ± 2 weeks	Every 24 weeks ± 2 weeks

[1]In general, the window for each visit is +/- 3 days unless otherwise noted. For patients who have to travel >50 miles for treatment, there will be a window of +/- 7 days for each visit.

[2]Written consent must be obtained prior to performing any protocol specific procedure. Results of a test performed prior to the subject signing consent as part of clinical management are acceptable in lieu of a screening test if performed within the specific time frame (e.g. within 28 days prior to study registration). Assign baseline number when the study informed consent is signed. A remote consent can be obtained if the patient lives >50 miles from the treatment site. The informed consent document can be sent by facsimile and/or through a secure email account. The consent interview can be performed by telephone and a signed consent form can be returned to the clinical investigator by facsimile and/or through a secure email account to protect the confidentiality of the subject. The patient must be re-consented in person prior to starting treatment.

[3]Prior medications – Record all medications taken within 28 days of study registration. Concomitant medications – Enter new medications started during the trial through the Safety Follow-up visit. Record all medications taken for SAEs as defined in Section 11.0.

[4]AEs and laboratory safety measurements will be graded per NCI CTCAE version 4.0. All AEs, whether gradable by CTCAE or not, will also be evaluated for seriousness.

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

[6]Full physical examination should be performed every 4 cycles after cycle 5. Otherwise, perform a directed physical examination the day of the study treatment visit.

[7]Vital signs to include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at visit 2 only.

[8]For women of reproductive potential, a serum pregnancy test should be performed within 72 hours prior to any dose of trial treatment.

[9]Coagulation factors (PT/INR and aPTT) should be tested as part of the screening procedures for all subjects. Any subject receiving anticoagulant therapy

Trial Period:	**Screening Phase**		**Treatment Cycles**								**End of Treatment (early or at 24 months)**	**Post-Treatment**		
							To be repeated beyond 8 cycles							
Treatment Cycle/Title:		Main Study Screening (Visit 1)	1	2	3	4	5	6	7	8	Discon	Safety Follow-up	Follow Up Visits[24]	Survival Follow-Up
Scheduling Window (Days)[1]:		-28 to -1		± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days post discon ± 2 weeks	Every 8 weeks post discon ± 2 weeks	Every 24 weeks ± 2 weeks

should have coagulation factors monitored closely throughout the trial.

[10]Laboratory tests for screening are to be performed within 28 days prior to study registration. See Section 10.1.3 for details regarding laboratory tests.

[11]After Cycle 1, lab samples can be collected up to 72 hours prior to the scheduled time point. See Section 10.1.3 for details regarding laboratory tests.

[12]To be repeated every 4 cycles.

[13]The initial tumor imaging will be performed within 28 days prior to study registration. Scans performed as part of routine clinical management are acceptable for use as the screening scan if they are of diagnostic quality and performed within 28 days prior to study registration. The initial tumor imaging study will be performed with intravenous contrast (unless the patient has an allergy to contrast) and subsequent scans will be performed without intravenous contrast.

[14]On-study radiographic imaging will be performed every 8 cycles (+/- 14 days) after the first dose of trial treatment. For those patients with pulmonary lesions measurable by RECIST 1.1, lymphadenopathy, or extra-tracheal disease (exception being the larynx), radiographic imaging will be obtained every 4 cycles (+/- 7 days). Per the 3-dimensional tracheal reconstruction volumetric measurement and/or modified RECIST 1.1 used in this protocol, if imaging shows progressive disease, repeat imaging assessment should be performed at a minimum of 4 weeks later in order to confirm progressive disease. Image timing should follow calendar days and should not be adjusted for delays in cycle starts. For patients who have to travel >50 miles for treatment, there will be a window of +/- 7 days for imaging.

[15]In subjects who discontinue study therapy without confirmed disease progression, a radiological and/or clinical imaging should be performed at the time of treatment discontinuation (i.e. date of discontinuation +/- 4 week window). If a previous scan was obtained within 4 weeks prior to the date of discontinuation, then a scan at treatment discontinuation is not mandatory.

[16]In subjects who discontinue study therapy (early or at 24 months) without documented disease progression, every effort will be made to continue monitoring their disease status by radiologic imaging every 6 months (+/- 2 weeks) until: 1) documented disease progression; 2) death; or 3) 36 months post study registration, whichever occurs first.

[17]Unresolved labs that are drug related AEs should be followed until resolution. Labs do not need to be repeated after the end of treatment if labs are within

Trial Period:	**Screening Phase**		**Treatment Cycles**								**End of Treatment (early or at 24 months)**	**Post-Treatment**		
							To be repeated beyond 8 cycles							
Treatment Cycle/Title:		Main Study Screening (Visit 1)	1	2	3	4	5	6	7	8	Discon	Safety Follow-up	Follow Up Visits[24]	Survival Follow-Up
Scheduling Window (Days)[1]:		-28 to -1		± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days post discon ± 2 weeks	Every 8 weeks post discon ± 2 weeks	Every 24 weeks ± 2 weeks

normal range.

[18]Tumor biopsy will be obtained only if there are lesions present.

[19]Tumor biopsy, blood for correlative studies for clinically stable subjects, and quality of life questionnaires should be obtained at treatment discontinuation.

[20]Survival status should be obtained at each clinic visit and/or each tumor assessment. Following first disease progression, subjects will be followed by telephone for overall survival until death, withdrawal of consent, or 36 months from study registration, whichever occurs first.

[21]Endoscopic evaluations at baseline should be done within 6 weeks prior to enrollment into the study.

[22]Clinical imaging assessed by laryngoscopy and tracheoscopy will be performed every 3 weeks (21 days+/- 3 days). In addition, a comprehensive laryngoscopy, tracheoscopy, and bronchoscopy will be performed every 4 cycles in the operating room.

[23]VHI-10 questionnaire is required only for subjects enrolled after IRB approval and/or activation of Protocol AM 10

[24]After 1 year, the clinical assessment will be reduced to 24 weeks for 12 months only.

9.2 Second Course Phase (Retreatment ONLY)

Trial Period:	Treatment Cycles[1]								End of Treatment	Post-Treatment		
					To be repeated beyond 8 cycles							
Treatment Cycle/Title:	1	2	3	4	5	6	7	8	Discon	Safety Follow-up	Follow Up Visits[2]	Survival Follow-Up
Scheduling Window (Days)[3]:		± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days post discon ± 2 weeks	Every 8 weeks post discon ± 2 weeks	Every 24 weeks ± 2 weeks
Administrative Procedures												
Eligibility Criteria[4]												
Concomitant Medication Review[5]	X	X	X	X	X	X	X	X	X	X[5]		
Trial Treatment Administration[6]	X	X	X	X	X	X	X	X				
Post-study anticancer therapy status											X	X[19]
Survival Status												X[19]
Clinical Procedures/Assessments												
Review Adverse Events[7]	X	X	X	X	X	X	X	X	X	X[8]	X[8]	
Full Physical Examination	X				X[9]							
Directed Physical Examination	X	X	X	X		X	X	X	X			
Vital Signs and Weight[11]	X	X	X	X	X	X	X	X	X			
ECOG Performance Status	X	X	X	X	X	X	X	X[12]	X			
Laboratory Procedures/Assessments:												
Pregnancy Test –Serum β-HCG[13]	X	X	X	X	X	X	X	X				
PT/INR and aPTT[14]	X[15]											
CBC with Differential[16]	X[15]	X	X	X	X	X	X	X	X	X[17]		
Comprehensive Serum Chemistry Panel[16]	X[15]	X	X	X	X	X	X	X	X	X[17]		
T3, FT4 and TSH[16]	X[15]			X[10]						X[17]		

Efficacy Measurements												
Radiographic Tumor Imaging[18]	X							X	X[19]		X[2]	X
Clinical Imaging: Video-recording of flexible fiberoptic laryngoscopy, tracheoscopy, and/or bronchoscopy examination	X	X	X	X	X	X	X	X	X	X	X	X
Tumor Biopsy[20]				X				X	X[21]			
Correlative Studies Blood Collection	X			X				X	X[21]			
Quality of Life Questionnaires[22]	X			X				X	X[21]			

[1]In general, assessments/procedures are to be performed on Day 1 and prior to the first dose of treatment for each cycle unless otherwise specificed. Treatment cycles are 3 weeks.

[2]In subjects who discontinue study therapy without documented disease progression, every effort should be made to continue monitoring their disease status by radiologic imaging until: 1) the start of new anti-cancer treatment, 2) documented disease progression, 3) death, or 4) the end of the study, whichever occurs first.

[3]In general, the window for each visit is $\pm$ 3 days unless otherwise noted. For patients who have to travel >50 miles for treatment, there will be a window of +/- 7 days

[4]Subjects who either: a) attain a CR and discontinue treatment or b) discontinue treatment after 24 months on pembrolizumab for reasons other than disease progression or intolerability may restart trial treatment if they meet the criteria specific in Section 10.1.5.5.

[5]Concomitant medications – Enter new medications started during the trial through the Safety Follow-up visit. Record all medications taken for SAEs as defined in Section 11.0.

[6]Subjects who restart treatment should resume at the same dose and cycle interval which they were receiving prior to discontinuation. Record all medications taken for SAEs as defined in Section 11.0.

[7]AEs and laboratory safety measurements will be graded per NCI CTCAE version 4.0. All AEs, whether gradable by CTCAE or not, will also be evaluated for seriousness.

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

[9]Following Cycle 8, the directed physical exam is only required at Cycle 11, 15, 18 and every 4 cycles thereafter.

[10]To be repeated every 4 cycles.

[11]Vital signs to include temperature, pulse, respiratory rate, weight, and blood pressure.

[12]Following Cycle 8, the ECOG performance status should be determined only in conjunction with a protocol-specified full or directed physical exam (Cycles 8, 11, 13, 15, 17, 19, and every 3 cycles thereafter.)

[13]For women of reproductive potential, a serum pregnancy test should be performed within 72 hours prior to any dose of trial treatment.

[14]Coagulation factors (PT/INR and aPTT) should be monitored closely throughout the trial for any subject receiving anticoagulant therapy.

[15]Laboratory tests for determining eligibility for retreatment are to be performed within 28 days prior to the first retreatment dose of pembrolizumab. See Section 10.1.3 for details regarding laboratory tests.[16]After the first dose, lab samples can be collected up to 72 hours prior to the scheduled time point. See Section 10.1.3 for details regarding laboratory tests.

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

[18]A scan must be performed within 28 days prior to restarting treatment with pembrolizumab. The initial tumor imaging study will be performed with intravenous contrast (unless the patient has an allergy to contrast) and subsequent scans will be performed without intravenous contrast. On-study radiographic imaging will be performed every 8 cycles (+/- 14 days) after the first dose of retreatment. For those patients with pulmonary lesions measurable by RECIST 1.1, lymphadenopathy, or extra-tracheal disease (exception being the larynx), radiographic imaging will be obtained every 4 cycles (+/- 7 days). Per the 3-dimensional tracheal reconstruction volumetric measurement and/or modified RECIST 1.1 used in this protocol, if imaging shows progressive disease, repeat imaging assessment should be performed at a minimum of 4 weeks later in order to confirm progressive disease. Image timing should follow calendar days and should not be adjusted for delays in cycle starts. For patients who have to travel >50 miles for treatment, there will be a window of +/- 7 days.

[19]In subjects who discontinue study therapy without confirmed disease progression, a radiological evaluation should be performed at the time of treatment discontinuation (i.e. date of discontinuation +/- 4 week window). If a previous scan was obtained within 4 weeks prior to the date of discontinuation, then a scan at treatment discontinuation is not mandatory. In subjects who discontinue study therapy (early or at 24 months) without documented disease progression, every effort will be made to continue monitoring their disease status by radiologic imaging every 6 months (+/- 2 weeks) until: 1) documented disease progression; 2) death; or 3) 36 months post study registration, whichever occurs first.

[20]Tumor biopsy will be obtained only if there are lesions present.

[21]Tumor biopsy, blood for correlative studies in clinically stable subjects, and quality of life questionnaires will be obtained at treatment discontinuation.

[22]VHI-10 questionnaire is required only for subjects enrolled after IRB approval and/or activation of Protocol AM 10

10.0 TRIAL PROCEDURES

10.1 Trial Procedures

The Trial Flow Chart - Section 9.0 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 Sponsor 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.

10.1.1 Administrative Procedures

10.1.1.1 Informed Consent

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

10.1.1.1.1 General Informed Consent

Consent must be documented by the subject's dated signature or by the subject's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion. A remote consent can be obtained if the subject lives >50 miles from the treatment site. The informed consent document can be sent by facsimile and/or through a secure email account. The consent interview can be performed by telephone and a signed consent form can be returned to the clinical investigator by facsimile and/or through a secure email account to protect the confidentiality of the subject. The patient must be re-consented in person prior to starting treatment.

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

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

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

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

10.1.1.2 Inclusion/Exclusion Criteria

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

10.1.1.3 Medical History

A medical history will be obtained by the treating investigator or qualified designee. Medical history will include all active conditions, and any condition diagnosed within the prior 10 years that are considered to be clinically significant by the Investigator. Details regarding the disease for which the subject has enrolled in this study will be recorded separately and not listed as medical history.

10.1.1.4 Prior Medications Review

The treating investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the subject within 28 days before starting the trial. Treatment for the disease for which the subject has enrolled in this study will be recorded separately and not listed as a prior medication.

10.1.1.5 Concomitant Medications Reviews

The treating investigator or qualified designee will record medication, if any, taken by the subject during the trial. All medications related to reportable SAEs and ECIs should be recorded as defined in Section 11.0.

10.1.1.6 Disease Details

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

10.1.1.7 Prior Treatment Details

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

10.1.1.8 Subsequent Therapy Status

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

10.1.1.9 Assignment of Screening Number

All consented subjects will be given a unique screening number that will be used to identify the subject for all procedures that occur prior to randomization or treatment allocation. Each subject will be assigned only one screening number. Screening numbers must not be re-used for different subjects. Any subject who is screened multiple times will retain the original screening number assigned at the initial screening visit.

10.1.1.10 Assignment of Randomization Number

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

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

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

Any interruptions from the protocol specified treatment plan due to toxicity will result in the patient withdrawing from treatment.

Administration of trial medication will be witnessed by the investigator and/or trial staff. The total volume of trial treatment infused will be compared to the total volume prepared to determine compliance with each dose administered.

10.1.2 Clinical Procedures/Assessments

10.1.2.1 Adverse Event (AE) Monitoring and Rapid Review Overview

The treating 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 throughout the study and during the follow-up period according to NCI CTCAE Version 4.0. Toxicities will be characterized in terms regarding causality, toxicity grading, and action taken with regard to trial treatment.

For subjects receiving treatment with pembrolizumab all AEs of unknown etiology associated with pembrolizumab exposure should be evaluated to determine if it is possibly an event of clinical interest (ECI) of a potentially immunologic etiology (termed immune-related adverse events, or irAEs); see the separate ECI guidance document in Appendix 4 regarding the identification, evaluation and management of potential irAEs.

Please refer to Section 11.0 for detailed information regarding the assessment and recording of AEs.

10.1.2.2 Full Physical Exam

The treating investigator or qualified designee will perform a complete physical exam during the screening period. Clinically significant abnormal findings should be recorded as medical history. A full physical exam should be performed during screening.

10.1.2.3 Directed Physical Exam

For cycles that do not require a full physical exam per the Trial Flow Chart, the treating investigator or qualified designee will perform a directed physical exam as clinically indicated prior to trial treatment administration. Patients will undergo a video-recorded transnasal flexible fiberoptic laryngoscopy and tracheoscopy examination within +/- 24 hours that they receive each dose of pembrolizumab. The treating surgeon will complete the Severity Scoring Sheets (found in Section 18.0A Surgical Scoring sheets) at each session and document procedure findings.

10.1.2.4 Vital Signs

The treating investigator or qualified designee will take vital signs at screening, prior to the administration of each dose of trial treatment and at treatment discontinuation as specified in the Trial Flow Chart (Section 9.0). Vital signs should include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at screening only.

10.1.2.5 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The treating investigator or qualified designee will assess ECOG status at screening, prior to the administration of each dose of trial treatment and discontinuation of trial treatment as specified in the Trial Flow Chart.

10.1.2.6 Tumor Imaging and Assessment of Disease

Clinical response rates will be the primary measure for assessment of tumor response and as a basis for all protocol guidelines related to disease status (e.g. discontinuation of study therapy). Clinical response will be assessed by direct visualization and scoring of disease burden within the upper aerodigestive tract (**Appendix A: Surgical Scoring and Appendix G: CRFs**).

The burden of disease will be assessed at each direct laryngoscopy/tracheoscopy examination performed in clinic and in the operating room, and the extent of papilloma growth will be measured using an instrument previously described [8, 9]. Briefly, evaluations will be made of five major anatomic sites in the larynx (epiglottis, false cords, ventricle, true cords, and subglottis), which are subdivided into 23 subsites. Four major anatomic sites in the tracheo-bronchial tree (trachea, tracheostomy site, if present, carina and mainstem bronchus) are divided into 6 subsites. The rating incorporates three components. Number of sites (AS) is the actual number of affected sites. For laryngeal disease, this value can range from 0 to 23. Surface area (SA) involvement at each major site is rated on the following scale: 0 (none), 1 (under 1/3 of area is affected), 2 (under 2/3 of area), or 3 (more than 2/3 of area). For the total of five major sites this value can range from 0 to 15. Extent of lumen obstruction (LO) reflects the degree of airway obstruction at each site, on a similar scale of 0-3. For the total of five major sites this

value can range from 0 to 15. The three components (AS, SA and LO) are summed to yield a single overall rating, but the scores are entered separately into the computer to permit analysis of separate components of the score if desired. The potential range of this scoring system is 0 to 53 for laryngeal disease; the range observed in previous studies was 0 to 43 (www.clinicaltrials.gov; NCT00571701). Scores for tracheobronchial disease are calculated similarly. The maximum possible AS score is 6. The maximum SA and LO scores are each 12. Therefore, the maximum summed score for tracheo-bronchial involvement is 30. Copies of the scoring sheet pages are included in the appendix, as part of the case report forms (**Appendix A: Surgical Scoring and Appendix G: CRFs)**.

To ensure protocol compliance and consistency among participating sites, a Rapid Review will be conducted. The videos from the screening clinic and operating room visit for each institution's first three cases will be reviewed by Dr. Sara Pai and the Site Investigator via a WebEx and Teleconference. Rapid Reviews will be conducted within 14 days of the surgery. Additional reviews may be requested by the Principal Investigator until protocol compliance is adequately demonstrated. Review will be arranged by the Coordinating Center as per procedures listed below:

Process for Endoscopic Video and Score Sheet Rapid Review:

1. At the time of registration, the Coordinating Center will identify if the patient is subject to Rapid Review.

2. Coordinating Center is notified of the date and time of the surgery to be reviewed for each case by the external sites. Video and score sheets will be sent per instructions below to the Coordinating Center.

3. Once the video and score sheet are reviewed, the PI and Site Investigator will review the video via a WebEx and teleconference arranged by the Coordinating Center.

4. Any issues identified during the review will be communicated, documented, and resolved at the time of review.

5. The Coordinating Center notifies the study team at the participating site that the review is complete and provides email confirmation to the study team.

De-identified videos of the endoscopic (laryngoscopy, tracheoscopy, and/or bronchoscopy) examination will be sent to the Coordinating Center every 4 cycles (at the time of surgical biopsy). Videos maybe downloaded onto a secure server and/or sent via a USB drive or CD labeled with two patient identifiers to the following address:

MGH CCPO Multi-Center Program
c/o Lisa Raeke-Program Manager
125 Nashua Street, #9424
Boston, MA 02114

Severity Scoring sheets should be submitted to the Coordinating Center in real time. PDFs of all sheets should be emailed to Dr. Sara Pai at sara.pai@mgh.harvard.edu **and** the MC Coordinator over a secure network. In subject header include study number (15-469) and patient's ID number and initials.

10.1.2.6.1 Assessment of Response

Overall response rates according to clinical assessment will be derived from time-point response assessments as follows:

- **Complete Response (CR):** Complete disappearance of all tumor lesions (and no new lesions). CR must be confirmed by repeated, consecutive assessments made no less than 4 weeks from the date first documented.
- **Partial Response (PR):** Decrease in the summed score for laryngeal and tracheo-bronchial involvement by 25% or greater by a consecutive assessment at least 4 weeks after first documentation.
- **Stable Disease (SD):** Failure to meet criteria for CR or PR, in absence of PD.
- **Progressive Disease (PD):** At least 25% increase in the summed score for laryngeal and tracheo-bronchial involvement, confirmation by a repeat, consecutive assessment no less than 4 weeks from the date first documented.

3-Dimension tracheal reconstruction with volumetric analysis and RECIST 1.1 will be applied as another measure for assessing tumor response in those patients with tracheal and/or pulmonary involvement, respectively, and will contribute to the basis for all protocol guidelines related to disease status (e.g. discontinuation of study therapy).

For those patients with pulmonary lesions measurable by RECIST 1.1, CT scans of the chest will be obtained every 12 weeks (84 days +/- 7 days) to assess response per RECIST 1.1 criteria. Imaging assessments will be adapted as follows to account for the unique tumor response seen in this class of therapeutics.

At the baseline imaging study, if there is no evidence of pulmonary disease measurable by RECIST 1.1, the patient will be followed with serial laryngoscopy/tracheoscopy examinations every 3 weeks and serial CT scans will be obtained every 6 months until the end of the study. If there is evidence of pulmonary disease, lymphadenopathy, and/or extra-tracheal disease (except those involving the larynx) measurable by RECIST 1.1, the patient will undergo repeat imaging every 12 weeks (± 7 days). If two consecutive imaging assessments demonstrate SD or CR, the patient will undergo repeat imaging every 6 months until the end of the study. If imaging shows PD, tumor assessment should be repeated no less than 4 weeks from the date first documented in order to confirm PD with the option of continuing treatment for clinically stable subjects as discussed below in the Table.

Clinically stable is defined by the following criteria:

*Absence of signs and symptoms indicating disease progression

* No decline in ECOG performance status

*Absence of rapid progression of disease

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

In determining whether or not the tumor burden has increased or decreased, all target lesions as well as non-target lesions should be considered. Subjects that are deemed clinically unstable are not required to have repeat imaging for confirmation. If radiologic progression is confirmed, then the subject will be discontinued from trial treatment. If radiologic progression is not confirmed, then the subject should resume/continue trial treatment and have their next scan in 12 weeks (84 ± 7 days).

After the first documentation of progression, it is at the discretion of the investigator to keep a clinically stable subject on trial treatment or to stop trial treatment until repeat imaging performed at least 28 days later confirms progression. When feasible, subjects should not be discontinued until progression is confirmed. Subjects that are deemed clinically unstable are not required to have repeat imaging for confirmation. If progression is confirmed, then the subject will be discontinued from trial treatment. If progression is not confirmed, then the subject should resume/continue trial treatment.

NOTE: *If a subject with confirmed radiographic progression (i.e. 2 scans at least 28 days apart demonstrating progressive disease) is clinically stable or clinically improved, and there is no further increase in the tumor dimensions at the confirmatory scan, an exception may be considered to continue treatment upon consultation with the Sponsor. Clinically stable subjects should also have at the confirmatory scan no further increase in the target lesions, no unequivocal increase in non-target lesions, and no additional new lesions develop (non-worsening PD) to continue study treatment.*

Imaging during the follow-up period is to be repeated every 6 months for subjects who discontinue trial treatment for reasons other than disease progression until the subject experiences confirmed disease progression or starts a new antineoplastic therapy.

Any new pulmonary findings on imaging which are not found to be clinically relevant or associated with RRP will be managed with standard guidelines and risk stratification of solitary pulmonary nodules.

10.1.2.7 Tumor Tissue Collection and Correlative Studies Blood Sampling

The natural clinical course of these subjects is the need for repeated operative procedures to debride recurrent growths of papillomatous lesions which may block the airway. A baseline tissue sample prior to starting systemic treatment will be collected. Subsequently, a tumor biopsy of one progressing and/or one regressing lesion, whenever possible and at the discretion of the surgeon, should be obtained at each operative visit which will occur at a minimum of every 12 weeks (84 days +/- 7 days) while on the study. If there are no lesions in the upper aerodigestive tract at the time of the operative examination, a biopsy will not be obtained. Some patients may require more frequent debridements based on the clinical symptoms and at the discretion of the surgeon and biopsies will be obtained at each operative visit. The tumor samples will be evaluated for changes in expression of various immune biomarkers which will include, but are not limited to: PD-1, PD-L1, PD-L2, CD4, CD8, FoxP3, CTLA-4, Lag-3, Tim-3, IFN-g, and HPV-specific CD8+ T cells.

Blood for correlative biomarker studies will be collected at baseline, at each cycle which corresponds with an operating room visit, and upon disease progression. The blood will be evaluated for changes in circulating HPV-specific CD8+ T cells and cytokines. For those patients eligible for a Second Course Phase (Retreatment), blood will also be collected on day 1 of the first cycle of re-treatment.

10.1.2.8 Quality of Life Questionnaires

Quality of life questionnaires will be completed prior to treatment and every fourth cycle thereafter until the end protocol treatment. (See Appendix F).

10.1.3 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below

Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

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

Table 5: Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Blood	Serum β-human chorionic gonadotropin†
Hemoglobin	Alkaline phosphatase	Glucose	(β-hCG)†
Platelet count	Alanine aminotransferase (ALT)	Protein	PT (INR)
WBC (total and differential)	Aspartate aminotransferase (AST)	Specific gravity	aPTT
Red Blood Cell Count	Lactate dehydrogenase (LDH)	Microscopic exam *(If abnormal)*	Total thriiodothyronine (T3)
Absolute Neutrophil Count	Carbon Dioxide ‡	results are noted	Free thyroxine (T4)
Absolute Lymphocyte Count	*(CO_2 or biocarbonate)*		Thyroid stimulating hormone (TSH)
	Uric Acid		
	Calcium		
	Chloride		Blood for correlative studies
	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 considered standard of care in your region.			

Laboratory tests for screening or entry into the Second Course Phase 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.

10.1.4 Other Procedures

10.1.4.1 Withdrawal/Discontinuation

When a subject discontinues/withdraws from protocol treatment and/or the study itself, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 11.0 - Assessing and Recording Adverse Events. Subjects who a) attain a CR or b) complete 24 months of treatment with pembrolizumab may discontinue treatment with the option of restarting treatment if they meet the criteria specified in Section 10.1.5.5. After discontinuing treatment following assessment of CR, these subjects should return to the site for a Safety Follow-up Visit (described in Section 10.1.5.3.1) and then proceed to the Follow-Up Period of the study (described in Section 10.1.5.4).

10.1.4.2 Blinding/Unblinding

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

10.1.5 Visit Requirements

Visit requirements are outlined in Section 9.0 - Trial Flow Chart. Specific procedure-related details are provided above in Section 10.1 - Trial Procedures.

10.1.5.1 Screening

10.1.5.1.1 Screening Period

Approximately 28 days prior to study registration, potential subjects will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5.1. Visit requirements are outlined in Section 9.0 – Trial Flow Chart.

Written consent for the main study must be obtained prior to performing any protocol specific procedure. Results of a test performed prior to the subject signing consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame. Screening procedures are to be completed within 28 days prior to study registration except for the following:

- For women of reproductive potential, a urine pregnancy test will be performed within 28 days prior to study registration. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required (performed by the local study site laboratory)

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

10.1.5.2 Treatment Period

On-study visits will occur on day 1 of each cycle of Pembrolizumab and will include the following at every visit:

1. Directed physical examination with flexible fiberoptic laryngoscopy and tracheoscopy
2. Review of concomitant medications
3. Vital signs to include temperature, pulse, respiratory rate, weight, and blood pressure.
4. Performance status evaluation
5. Determination adverse events
6. Serum pregnancy test for women of reproductive potential
7. Quality of Life Questionnaires will be done every fourth cycle
8. Laboratory studies: CBC with differential, serum chemistries, liver function tests starting on day 1 of Cycle 2
9. Urinalysis and TSH and Free T4 will be done every fourth cycle
10. CT scans of chest and abdomen will be done during cycle 8
11. Correlative blood collection on Day 1 of each Cycle that corresponds to an operating room visit.

After clinically evident progression the patient will be seen for a study visit, at which the following will be addressed:

1. Directed physical examination with flexible fiberoptic laryngoscopy and tracheoscopy
2. Review of concomitant medications
3. Performance status evaluation
4. Determination adverse events
5. Laboratory studies: CBC with differential, serum chemistries, liver function tests, unrinalysis, T3, FT4, and TSH

Fresh tumor specimens will be obtained if feasible during therapy if the patient undergoes examination under general anesthesia and/or debridement for a standard-of-care clinical purposes per the study flow chart.

10.1.5.3 Post-Treatment Visits

10.1.5.3.1 Safety Follow-Up Visit

The mandatory Safety Follow-Up Visit should be conducted approximately 30 days after the last dose of trial treatment or before the initiation of a new anti-cancer treatment, whichever comes first. All AEs that occur prior to the Safety Follow-Up Visit should be recorded. Subjects with an AE of Grade > 1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new anti-neoplastic therapy, whichever occurs first. SAEs that occur within 90 days of the end of treatment or before initiation of a new anti-cancer treatment should also be followed, recorded and reported. Subjects who are eligible for retreatment with pembrolizumab (as described in Section 10.1.5.5) may have up to two safety follow-up visits, one after the Treatment Period and one after the Second Course Phase.

10.1.5.4 Follow-up Visits

Subjects who discontinue trial treatment for a reason other than disease progression will move into the Follow-Up Phase and should be assessed every 8 weeks (56 days $\pm$ 7 days) by clinical examination and 6 months ($\pm$ 2 weeks) by radiologic imaging to monitor disease status. After 1 year, the clinical assessment will be reduced to 24 weeks for up to 12 months and CT imaging will not be required. Every effort should be made to collect information regarding disease status until the start of new anti-neoplastic therapy, disease progression, death, 36 months post study registration, or if the subject begins retreatment with pembrolizumab as detailed in Section 10.1.5.5. Information regarding post-study anti-neoplastic and/or anti-viral treatment will be collected if new treatment is initiated.

Subjects who are eligible to receive retreatment with pembrolizumab will move from the follow-up phase to the Second Course Phase when they experience disease progression. Details are provided in Section 9.2 – Trial Flow Chart for Re-treatment.

10.1.5.4.1 Survival Follow-up

Once a subject experiences confirmed disease progression, the subject moves into the survival follow-up phase and should be contacted by telephone every 24 weeks to assess for survival status until death, withdrawal of consent, or 36 months post study registration, whichever occurs first.

10.1.5.5 Second Course Phase (Retreatment Period)

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

EITHER:

- Stopped initial treatment with pembrolizumab after attaining an investigator-determined confirmed CR according to RECIST 1.1, and

- Was treated for at least 24 weeks with pembrolizumab before discontinuing therapy
- Received at least two treatments with pembrolizumab beyond the date when the initial CR was declared

OR:

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

AND:

- Experienced an investigator-determined confirmed clinical and/or radiographic disease progression after stopping their initial treatment with pembrolizumab
- Did not receive any anti-cancer treatment since the last dose of pembrolizumab
- Has a performance status of 0 or 1 on the ECOG Performance Scale
- Demonstrates adequate organ function as detailed in Section 5.1.2
- Female subject of childbearing potential should have a negative serum or urine pregnancy test within 28 days. (Please refer to the study calendar for requirements regarding a pregnancy test 72 hours prior to receiving any dose of study medication upon subject enrollment into the study.)
- Female subject of childbearing potential should be willing to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study medication (Reference Section 5.7.2). Subjects of child bearing potential are those who have not been surgically sterilized or have been free from menses for > 1 year.
- Male subject should agree to use an adequate method of contraception starting with the first dose of study therapy through 120 days after the last dose of study therapy.
- Does not have a history or current evidence of any condition, therapy, or laboratory abnormality that might interfere with the subject's participation for the full duration of the trial or is not in the best interest of the subject to participate, in the opinion of the treating investigator.

Subjects who restart treatment will be retreated at the same dose and dose interval as when they last received pembrolizumab. Treatment will be administered for up to one additional year.

11.0 ADVERSE EVENT REPORTING REQUIREMENT

11.1 General

Adverse event collection and reporting is a routine part of every clinical trial. This study will use the descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v4.0) that is available at http://ctep.cancer.gov/reporting//ctc.html.

Information on all adverse events, whether reported by the participant, directly observed, or detected by physical examination, laboratory test or other means, will be collected, recorded, followed and reported as described in the following sections.

Adverse events experienced by participants will be collected and reported from signing of consent, throughout the study, and within 30 days of the last dose of study medication. Participants who experience an ongoing adverse event or related to study procedures and/or study medication beyond 30 days will continue to be contacted by a member of the study team until the event is resolved, stabilized, or determined to be irreversible by the participating investigator.

Participants should be instructed to report any serious post-study event(s) that might reasonably be related to participation in this study. The investigator should notify the IRB and any other applicable regulatory agency of any unanticipated death or adverse event occurring after a participant has discontinued or terminated study participation that may reasonably be related to the study.

11.2 Adverse Event Definition

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

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

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.

Progression of the cancer under study is not considered an adverse event unless it is considered to be drug related by the investigator.

All adverse events will be recorded from the time the consent form is signed through 30 days following cessation of treatment and at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in Section 11.0.

11.3 Serious Adverse Events

A serious adverse event is any untoward medical occurence at any dose or that:

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

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

Events **not** considered to be serious adverse events are hospitalizations for:

- routine treatment or monitoring of the studied indication, not associated with any deterioration in condition, or for elective procedures
- treatment planned before signing informed consent for a pre-existing condition that did not worsen
- emergency outpatient treatment for an event not fulfilling the serious criteria outlined above and not resulting in inpatient admission
- respite care
- Abnormal lab values that do not require medical intervention to return to baseline value

Progression of the cancer under study is not considered an adverse event unless it results in hospitalization or death.

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

11.4 Evaluating Adverse Events

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

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

The causality of SAEs (their relationship to all study treatment/procedures) and the expectedness

will be assessed by the treating investigator(s) and communicated to the Sponsor-Investigator. The causal relationship can be one of the following:

- Related: There is a reasonable causal relationship between study drug administration and the AE.
- Not Related: There is not a reasonable causal relationship between study drug administration and the AE.

Table 6: Evaluating Adverse Events

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 a condition of the study) **or**	
	Is an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours.	
	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	
Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the adverse event cause the 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 U.S. CLINICAL MONITOR 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 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.)

11.5 Expedited Adverse Event Reporting

Investigators must report to the Coordinating Center and Overall PI any serious adverse event (SAE) that occurs after the initial dose of study treatment, during treatment, or within 90 days of the last dose of treatment.

11.5.1 Reporting Requirements

For multi-institution studies where a DF/HCC investigator is serving as the Overall Principal Investigator, each participating institution must abide by the reporting requirements set by the DF/HCC. In addition to SAEs that meet criteria set forth in Section 11.3, the Sponsor requires reporting of any medical event equivalent to an unexpected grade 2 or 3 with a possible, probable or definite attribution, unexpected grade 4 toxicities, and grade 5 (death) regardless of study phase or attribution.

Each investigative site will be responsible to report SAEs that occur at that institution to their respective IRB. It is the responsibility of each participating investigator to report serious adverse events to the study sponsor and/or others as described below.

11.5.2 Reporting to the Sponsor

Investigative sites within DF/HCC will report AEs directly to the DFCI Office for Human Research Studies (OHRS) per the DFCI IRB reporting policy.

Other investigative sites will report AEs to their respective IRB according to the local IRB's policies and procedures in reporting adverse events. A copy of the submitted institutional AE form should be forwarded to the Coordinating Center within the timeframes detailed in the table below.

	DF/HCC Reportable AEs				
Attribution	**Gr. 2 & 3 AE Expected**	**Gr. 2 & 3 AE Unexpected**	**Gr. 4 AE Expected**	**Gr. 4 AE Unexpected**	**Gr. 5 AE Expected or Unexpected**
Unrelated Unlikely	Not required	Not required	5 calendar days[#]	5 calendar days	24 hours*
Possible Probable Definite	Not required	5 calendar days	5 calendar days[#]	5 calendar days	24 hours*
# If listed in protocol as expected and not requiring expedited reporting, event does not need to be reported.					
* For participants enrolled and actively participating in the study ***or*** for AEs occurring within 30 days of the last intervention, the AE should be reported within 1 business day of learning of the event.					

Participating investigators must report each serious adverse event to the Coordinating Center in accordance with the table above. In the event that the participating investigator does not become aware of the serious adverse event immediately (e.g., participant sought treatment elsewhere) or within the reporting timeframes listed in the table above, the participating investigator is to

report the event within 1 business day after learning of it and document the time of his or her first awareness of the adverse event. Report serious adverse events by email or facsimile to:

Coordinating Center
Fax: 617-724-2787

The Coordinating Center will submit AE reports from outside institutions to the DFCI OHRS according to DFCI IRB policies and procedures in reporting adverse events.

11.5.3 Reporting to Merck

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 consent is signed 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 24 hours to the Coordinating Center and within 2 working days to Merck Global Safety.

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 Coordinating Center and to Merck.

A copy of all 15 Day Reports and Annual Progress Reports is submitted as required by FDA, European Union (EU), Pharmaceutical and Medical Devices agency (PMDA) or other local regulators. Investigators will cross reference this submission according to local regulations to the Merck Investigational Compound Number (IND, CSA, etc.) at the time of submission. Additionally investigators will submit a copy of these reports at the time of submission to FDA.

The Coordinating Center will submit all SAE reports, 15 day reports, FDA reports and any other relevant safety information to Merck & Co., Inc on behalf of the Sponsor at:

Merck Global Safety
Attn: Worldwide Product Safety
Fax number: +1-215-661-6229

11.5.4 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be recorded as such on the Adverse Event case report forms/worksheets and reported within 24 hours to the Coordinating Center and within 2 working days to Merck Global Safety. The Coordinating Center will submit all safety reports to Merck on behalf of the Sponsor.

Events of clinical interest for this trial include:

1. An overdose of Merck product, as defined in Section 11.5.5 - Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor, that is not associated with clinical symptoms or abnormal laboratory results.

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

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

3. Additional adverse events:

   A separate guidance document has been provided entitled "Event of Clinical Interest Guidance Document" (previously entitled, "Event of Clinical Interest and Immune-Related Adverse Event Guidance Document"). This document can be found in Appendix 4 and provides guidance regarding identification, evaluation and management of ECIs and irAEs.

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

   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.

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

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."

All reports of overdose with and without an adverse event must be reported within 24 hours to the Coordinating Center and within 2 working days hours to Merck Global Safety. The Coordinating Center will submit all safety reports to Merck on behalf of the Sponsor.

11.5.6 Reporting of Pregnancy and Lactation to the Sponsor and to Merck

Although pregnancy and lactation are not considered adverse events, it is the responsibility of traeting 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 the trial or within 120 days of completing the trial completing the trial, or 30 days following cessation of 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. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Such events must be reported within 24 hours to the Coordinating Center and within 2 working days to Merck Global Safety. The Coordinating Center will submit all safety reports to Merck on behalf of the Sponsor.

11.5.7 Sponsor Responsibility for Reporting Adverse Events

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

11.5.8 Institutional Review Board (IRB) Notification by Investigator

The participating investigator will report all adverse events and serious adverse events to the Coordinating Center and to the IRB according to the local IRB's policies and procedures in reporting adverse events.

11.5.9 Food and Drug Administration (FDA) Notification by Sponsor-Investigator

The Overall PI, as study sponsor, will be responsible for all communications with the FDA. The Coordinating Center, on behalf of the Sponsor, will report to the FDA any adverse event that is serious, unexpected and reasonably related (i.e., possible, probable, definite) to the study treatment.

Unexpected fatal or life-threatening experiences associated with the use of the study treatment will be reported to the FDA as soon as possible but in no event later than 7 calendar days after initial receipt of the information.

All other serious unexpected experiences associated with the use of the study treatment will be reported to the FDA as soon as possible but in no event later than 15 calendar days after initial receipt of the information.

Events will be reported to the FDA by telephone (1-800-FDA-1088) or by fax (1-800-FDA-0178) using Form FDA 3500A (Mandatory Reporting Form for investigational agents) or FDA Form 3500 (Voluntary Reporting Form for commercial agents). Forms are available at http://www.fda.gov/medwatch/getforms.htm.

11.5.10 NIH Office of Biotechnology Activities (OBA) Notification by Investigator

Not applicable

11.5.11 Institutional Biosafety Committee (IBC) Notification by Investigator

Not applicable

11.5.12 Hospital Risk Management Notification by Investigator

The participating investigator will report to the Coordinating Center and to local Risk Management any subject safety reports or sentinel events that require reporting according to institutional policy.

11.6 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions to the Overall PI on the toxicity case report forms. **AEs reported through expedited processes (e.g., reported to the IRB, FDA, etc.) must also be reported in routine study data submissions.**

12.0 DATA AND SAFETY MONITORING

12.1 Data Reporting

12.1.1 Method

The DF/HCC Office of Data Quality (ODQ) will collect, manage, and audit data for this study.

12.1.2 Data Submission

The schedule for completion and submission of case report forms (paper or electronic) to the ODQ is as follows:

Form	Submission Timeline
Eligibility Checklist	Complete prior to registration
On Study Form	Within 14 days of registration
Baseline Assessment Form	Within 14 days of registration
Treatment Form	Within 10 days of the last day of the cycle
Adverse Event Report Form	Within 10 days of the last day of the cycle
Response Assessment Form	Within 10 days of the completion of the cycle required for response evaluation
Off Treatment/Off Study Form	Within 14 days of completing treatment or being taken off study for any reason
Follow up/Survival Form	Within 14 days of the protocol defined follow up visit date or call

12.2 Data Safety Monitoring

The DF/HCC Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this trial. The committee is composed of clinical specialists with experience in oncology and who have no direct relationship with the study. Information that raises any questions about participant safety will be addressed with the Principal Investigator and study team.

The DSMC will meet approximately quarterly and/or more often if required to review toxicity and accrual data. Information to be provided to the committee may include: up-to-date participant accrual; current dose level information; all grade 2 or higher unexpected adverse events that have been reported; summary of all deaths occurring within 30 days for Phase I or II protocols; summary of all deaths while being treated and during active follow-up; any response information; audit results, and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

12.3 Multi-center Guidelines

This protocol will adhere to the policies and requirements of the DF/HCC Multi-Center Data and Safety Monitoring Plan. The specific responsibilities of the Overall PI, Coordinating Center, and Participating Institutions and the procedures for auditing are presented in Appendix I.

- The Overall PI/Coordinating Center is responsible for distributing all IND Action Letters or Safety Reports to all participating institutions for submission to their individual IRBs for action as required.
- Mechanisms will be in place to ensure quality assurance, protocol compliance, and adverse event reporting at each site.

- Except in very unusual circumstances, each participating institution will order the study agent(s) directly from supplier. A participating site may order the agent(s) only after the initial IRB approval for the site has been forwarded to the Coordinating Center.

12.4 Monitoring

Involvement in this study as a participating investigator implies acceptance of potential audits or inspections, including source data verification, by representatives designated by the Principal Investigator (or Protocol Chair) or DF/HCC. The purpose of these audits or inspections is to examine study-related activities and documents to determine whether these activities were conducted and data were recorded, analyzed, and accurately reported in accordance with the protocol, institutional policy, Good Clinical Practice (GCP), and any applicable regulatory requirements.

All data will be monitored for timeliness of submission, completeness, and adherence to protocol requirements. Monitoring will begin at the time of participant registration and will continue during protocol performance and completion.

13.0 REGULATORY CONSIDERATIONS

13.1 Protocol Review and Amendments

This protocol, the proposed informed consent and all forms of participant information related to the study (e.g., advertisements used to recruit participants) and any other necessary documents must be submitted, reviewed and approved by a properly constituted IRB governing each study location.

Any changes made to the protocol must be submitted as amendments and must be approved by the IRB prior to implementation. Any changes in study conduct must be reported to the IRB. The Principal Investigator (or Protocol Chair) will disseminate protocol amendment information to all participating investigators.

All decisions of the IRB concerning the conduct of the study must be made in writing.

13.2 Informed Consent

All participants must be provided a consent form describing this study and providing sufficient information for participants to make an informed decision about their participation in this study. The formal consent of a participant, using the IRB approved consent form, must be obtained before the participant is involved in any study-related procedure. The consent form must be signed and dated by the participant or the participant's legally authorized representative, and by the person obtaining the consent. A remote consent can be obtained if the subject lives >50 miles from the treatment site. The informed consent document can be sent by facsimile and/or through a secure email account. The consent interview can be performed by telephone and a signed consent form can be returned to the clinical investigator by facsimile and/or through a secure email account to protect the confidentiality of the subject. The patient must be re-consented in

person prior to starting treatment. The participant must be given a copy of the signed and dated consent document before participation in the trial. The original signed copy of the consent document must be retained in the medical record or research file.

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.

13.3 Ethics and Federal Regulations

This study is to be conducted according to the following considerations, which represent good and sound research practice:

- US Code of Federal Regulations (CFR) governing clinical study conduct and ethical principles that have their origin in the Declaration of Helsinki
  - Title 21 Part 50 – Protection of Human Subjects www.access.gpo.gov/nara/cfr/waisidx_02/21cfr50_02.html
  - Title 21 Part 54 – Financial Disclosure by Clinical Investigators www.access.gpo.gov/nara/cfr/waisidx_02/21cfr54_02.html
  - Title 21 Part 56 – Institutional Review Boards www.access.gpo.gov/nara/cfr/waisidx_02/21cfr56_02.html
  - Title 21 Part 312 – Investigational New Drug Application www.access.gpo.gov/nara/cfr/waisidx_02/21cfr312_02.html
- State laws
- Institutional research policies and procedures: www.dfhcc.harvard.edu/clinical-research-support/clinical-research-operations-cro/policies-and-procedures

It is understood that deviations from the protocol should be avoided, except when necessary to eliminate an immediate hazard to a research participant. In such case, the deviation must be reported to the IRB according to the local reporting policy.

13.4 Study Documentation

The investigator must prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each research participant. This information enables the study to be fully documented and the study data to be subsequently verified.

Original source documents supporting entries in the case report forms include but are not limited to hospital records, clinical charts, laboratory and pharmacy records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, and/or x rays.

13.5 Records Retention

All study-related documents must be retained for the maximum period required by applicable federal regulations and guidelines or institutional policies.

13.6 Cooperative Research and Development Agreement (CRADA)/Clinical Trials Agreement (CTA)

Not applicable

14.0 STATISTICAL ANALYSIS PLAN

14.1 Statistical Analysis Plan Summary

The primary endpoint of this trial is to evaluate the overall response rate (ORR:CR+PR) via clinical assessment and/or RECIST criteria for adult patients with measurable disease on CT scan. A Simon two-stage design will be used to minimize the number of adult patients exposed to this regimen and the specific sample size and operating characteristics were chosen to be able to rule out a 15% response rate. The rate chosen for the null hypothesis is based on several considerations:

1) There is no effective therapy for the patient population in this protocol.
2) This protocol represents the first time that this patient population will receive a systemic treatment option.
3) The response rate observed using the regimen under study in this protocol in patients with HPV positive head and neck cancer [10] was 20% with corresponding exact 95% CI (5.7% to 43.7%) and although it is anticipated that the patients in this protocol with benign tumors could experience a higher RR since their tumors are chemotherapy and/or RT naïve, this is still unknown.

In the first stage, accrual will continue until 11 evaluable adult patients are entered. If there are ≤1 adult patients whose disease shows best overall response of CR/PR, accrual to this trial will be closed with the expectation that there is little evidence that the RR would reach 38%. The probability that the trial will close early is 49% if the true RR is 15%. If there are ≥2 adult patients whose disease shows best overall response of CR/PR, accrual will continue until a total of 21 adult evaluable patients who started protocol treatment are entered. If there are ≥6 adult patients among 21 evaluable whose disease shows best overall response of CR/PR, further testing of this regimen will be considered. If the true response rate is 38%, the probability of concluding the regimen is effective is 86%, if the true response rate is 15%, the probability of concluding the regimen is effective is 8%. Allowing 1 adult patient to not begin protocol

treatment or be classified as ineligible, a total of 22 adult patients will be entered. In addition, approximately 2-3 pediatric patients will be entered as an exploratory cohort.

The primary efficacy population includes all eligible adult patients who begin protocol treatment. ORR will be summarized as a proportion with corresponding exact 95% confidence interval (CI) (if the trial closes to accrual after the first stage), or a corresponding 95% two-stage CI if the trial closes to accrual after the second stage. Best overall response for the pediatric patients will also be summarized.

Another endpoint is to assess adverse events. Adverse events will be classified and graded according to the CTCAE v.4.0. Frequencies of adverse events will be summarized overall and within adult and pediatric subgroups. Another endpoint is to assess quality of life (QOL). QOL will be assessed via self-report questionnaires at the timepoints outlined in the Study Flow Chart. Descriptive statistics from the questionnaires will be summarized across timepoints of assessment overall and within adult and pediatric subgroups. Rates of drop-out/non-response to QOL assessments and corresponding reason will also be summarized across timepoints of assessment. Secondary objectives include assessment of biomarkers in blood and tissue. Descriptive statistics from the assays will be summarized across timepoints of sample collection overall and within adult and pediatric subgroups. Rates of refusal and/or reason sample not obtained will be summarized across timepoints of assessment.

Various correlative studies will also be performed. Tissue and blood will be collected at baseline and at post-baseline timepoints as outlined in Section 9 and 10.1.2.7. Markers from tissue and blood will be summarized descriptively and graphically overall and within adult and pediatric subgroups. Within subject changes in markers will also be analyzed. Twenty-two adult patients with baseline and a post-baseline values provides 80% power to detect .65 SD mean difference (Wilcoxon sign rank test two-sided 0.05 alpha level). Baseline as well as changes from baseline to a post-baseline timepoint will also be compared between patients whose disease responded (CR,PR) and those whose disease did not respond using the Wilcoxon rank-sum test . Twenty two adult patients provides 82% power (using a two-sided 0.05 alphas level test) to detect a 1.4 SD difference in means assuming that 38% of the patients have disease which responds.

With an estimated monthly accrual of 1, the first stage is estimated to complete accrual in approximately 12 months. As is customary with this type of design, accrual will be suspended after the first stage (n=11 evaluable adult patients) in order to assess outcome, however, this suspension is also dependent on the actual observed accrual rate and the number of patients with best response confirmed for their disease while the first stage of the trial is accruing.

15.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

15.1 Investigational Product

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

Clinical Supplies will be provided by 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

15.2 Ordering Investigational Product

Participating institutions should order their own investigational product using the Merck Drug Order Request found in the Appendix H.

15.3 Packaging and Labeling Information

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

15.4 Clinical Supplies Disclosure

This trial is open-label; therefore, the subject, the trial site personnel, the Sponsor 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.

15.5 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.

15.6 Returns and Reconciliation

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

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.

16.0 ADMINISTRATIVE AND REGULATORY DETAILS

16.1 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the Sponsor of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to the Clinical Trials Data Bank, http://www.clinicaltrials.gov. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

16.1 Quality Management System

A quality management system with written development procedures and functional area standard operating procedures (SOPs) will be implemented and maintained to ensure that trials are conducted and data are generated, documented, and reported in compliance with the protocol and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the clinical trial.

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18.0 APPENDICES

A. Surgical Scoring

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TRIAL OF DRUG THERAPY FOR RECURRENT RESPIRATORY PAPILLOMATOSIS

DATE OF VISIT: ___ / ___ / _____	SITE: _____	PATIENT NUMBER: ___ ___ ___ - ___ ___ ___	PATIENT INITIALS: ___ ___

DATE OF SURGERY:	SURGEON:

Visit Number *(Circle One)*: Baseline 1 2 3 4 5 6 7 8 9 10

❑ Check if unscheduled surgery, do not circle visit number

❑ Check if waived surgery

SEVERITY SCORING SHEETS (page 1 of 6)

METHOD OF EVALUATION AND DOCUMENTATION	YES	NO
Direct Laryngoscopy	❑	❑
Direct Bronchoscopy	❑	❑
Indirect Laryngoscopy	❑	❑
Endoscopic photos (laryngoscopy)	❑	❑
Endoscopic photos (bronchoscopy)	❑	❑

None ☐

Laryngeal Sites of Clinical Papilloma

Epiglottis
- Lingual ☐
- Laryngeal ☐

Ventricle
- Right Posterior ☐
- Right Anterior ☐
- Left Posterior ☐
- Left Anterior ☐

Anterior Commissure
- Right ☐
- Left ☐

Arytenoids
- Right ☐
- Left ☐
- Inter ☐

A. Total # laryngeal sites with papillomas: ☐ (between 0-23)

False Cords
- Right Posterior ☐
- Right Anterior ☐
- Left Posterior ☐
- Left Anterior ☐

True Cords
- Right Posterior ☐
- Right Anterior ☐
- Left Posterior ☐
- Left Anterior ☐

Subglottis
- Right Posterior ☐
- Right Anterior ☐
- Left Posterior ☐
- Left Anterior ☐

None: ☐

Laryngeal Treatment Sites

Epiglottis
- Lingual ☐
- Laryngeal ☐

Ventricle
- Right Posterior ☐
- Right Anterior ☐
- Left Posterior ☐
- Left Anterior ☐

Anterior Commissure
- Right ☐
- Left ☐

Arytenoids
- Right ☐
- Left ☐
- Inter ☐

False Cords
- Right Posterior ☐
- Right Anterior ☐
- Left Posterior ☐
- Left Anterior ☐

True Cords
- Right Posterior ☐
- Right Anterior ☐
- Left Posterior ☐
- Left Anterior ☐

Subglottis
- Right Posterior ☐
- Right Anterior ☐
- Left Posterior ☐
- Left Anterior ☐

Papilloma remaining after treatment? Y: ☐ N: ☐

Intraoperative steroids used? Y: ☐ N: ☐

Site(s) of remaining papilloma _____

Name surgical instrument(s) used _____

TRIAL OF DRUG THERAPY FOR RECURRENT RESPIRATORY PAPILLOMATOSIS

DATE OF VISIT:	SITE:	PATIENT NUMBER:	PATIENT INITIALS:
___ / ___ / _____	_____	___ ___ ___ - ___ ___ ___	___ ___

SEVERITY SCORING SHEETS (page 2 of 6)

Laryngeal Biopsy Sites, Clinical Papilloma

None ☐

Epiglottis
- Lingual ☐
- Laryngeal ☐

Ventricle
- Right Posterior ☐
- Right Anterior ☐
- Left Posterior ☐
- Left Anterior ☐

Anterior Commissure
- Right ☐
- Left ☐

Arytenoids
- Right ☐
- Left ☐
- Inter ☐

False Cords
- Right Posterior ☐
- Right Anterior ☐
- Left Posterior ☐
- Left Anterior ☐

True Cords
- Right Posterior ☐
- Right Anterior ☐
- Left Posterior ☐
- Left Anterior ☐

Subglottis
- Right Posterior ☐
- Right Anterior ☐
- Left Posterior ☐
- Left Anterior ☐

Laryngeal Biopsy Sites, Adjacent Laryngeal Tissues

None: ☐

Epiglottis
- Lingual ☐
- Laryngeal ☐

Ventricle
- Right Posterior ☐
- Right Anterior ☐
- Left Posterior ☐
- Left Anterior ☐

Anterior Commissure
- Right ☐
- Left ☐

Arytenoids
- Right ☐
- Left ☐
- Inter ☐

False Cords
- Right Posterior ☐
- Right Anterior ☐
- Left Posterior ☐
- Left Anterior ☐

True Cords
- Right Posterior ☐
- Right Anterior ☐
- Left Posterior ☐
- Left Anterior ☐

Subglottis
- Right Posterior ☐
- Right Anterior ☐
- Left Posterior ☐
- Left Anterior ☐

TRIAL OF DRUG THERAPY FOR RECURRENT RESPIRATORY PAPILLOMATOSIS

DATE OF VISIT:	SITE:	PATIENT NUMBER:	PATIENT INITIALS:
___ / ___ / _____	_____	___ ___ ___ - ___ ___ ___	___ ___

SEVERITY SCORING SHEETS (page 3 of 6)

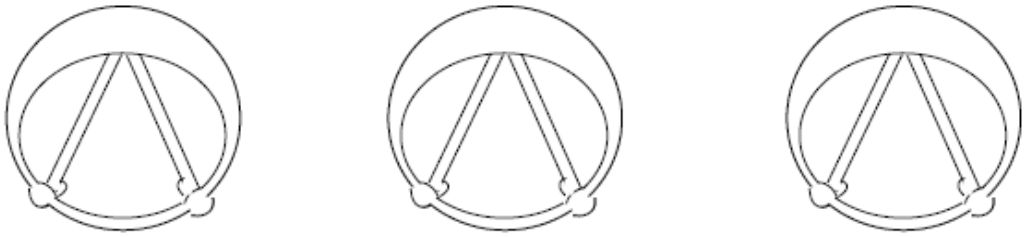
Visit Number *(Circle One)*: **Baseline 1 2 3 4 5 6 7 8 9 10**

❑ **Check if unscheduled surgery, do not circle visit number**

❑ **Check if waived surgery**

Please document laryngeal sites by marking diagrams accordingly:

Clinical Papilloma | Biopsy Sites of Papilloma | Biopsy Sites of Adjacent Tissue



Please circle appropriate numbers, using these criteria:
0= No involvement or obstruction
1= <1/3 involvement or obstruction
2= 1/3-2/3 involvement or obstruction
3= >2/3 involvement or obstruction

	Surface Area Involved (SA)	Extent of Lumen Obstruction (LO)
Epiglottis	0 1 2 3	0 1 2 3
False Cords	0 1 2 3	0 1 2 3
Ventricle	0 1 2 3	0 1 2 3
True Cords	0 1 2 3	0 1 2 3
Subglottis	0 1 2 3	0 1 2 3
Sum of Scores	SA Scores:_____	LO Scores: _____

B: Grand Total (Sum SA and LO scores): ☐ (between 0-30)

Calculation of Laryngeal Growth Rate: $\frac{\textbf{Score A (from pg. 18) + Score B}}{\textbf{Number days since last surgery}}$ = ☐

Date last Surgery: ___/___/____ (MM DD YYYY)

Use to calculate initial eligibility score

Comments: _____

TRIAL OF DRUG THERAPY FOR RECURRENT RESPIRATORY PAPILLOMATOSIS

DATE OF VISIT: ___ / ___ / _____	SITE: _____	PATIENT NUMBER: ___ ___ ___ - ___ ___ ___	PATIENT INITIALS: ____ ____

SEVERITY SCORING SHEETS (page 4 of 6)

Sites of Clinical Papilloma, Tracheo-Bronchial Region

None: ☐

Trachea
- Posterior ☐
- Anterior ☐

Bronchus
- Right ☐
- Left ☐

Tracheotomy site ☐

A. Total # of tracheo-bronchial sites: ☐ (between 0-5)

Treatment Sites, Tracheo-Bronchial Region

None: ☐

Trachea
- Posterior ☐
- Anterior ☐

Bronchus
- Right ☐
- Left ☐

Tracheotomy site ☐

Papilloma remaining after treatment? Y: ☐ N: ☐

Site(s) of remaining papilloma _____

Is there a tracheotomy present? Y: ☐ ☐

TRIAL OF DRUG THERAPY FOR RECURRENT RESPIRATORY PAPILLOMATOSIS

DATE OF VISIT:	SITE:	PATIENT NUMBER:	PATIENT INITIALS:
___ / ___ / _____	_____	___ ___ ___ - ___ ___ ___	___ ___

SEVERITY SCORING SHEETS (page 5 of 6)

Tracheo-Bronchial Biopsy Sites of Clinical Papilloma

None: ☐

Trachea
- Posterior ☐
- Anterior ☐

Bronchus
- Right ☐
- Left ☐

Tracheotomy site ☐

Tracheo-Bronchial Biopsy Sites of Adjacent Tissues

None: ☐

Trachea
- Posterior ☐
- Anterior ☐

Bronchus
- Right ☐
- Left ☐

Tracheotomy site ☐

TRIAL OF DRUG THERAPY FOR RECURRENT RESPIRATORY PAPILLOMATOSIS

DATE OF VISIT: ___ / ___ / _____	SITE: _____	PATIENT NUMBER: ___ ___ ___ - ___ ___ ___	PATIENT INITIALS: ____ ____

SEVERITY SCORING SHEETS (page 6 of 6)

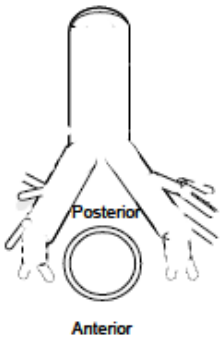
Visit Number *(Circle One)*: **Baseline 1 2 3 4 5 6 7 8 9 10**

❑ **Check if unscheduled surgery, do not circle visit number**

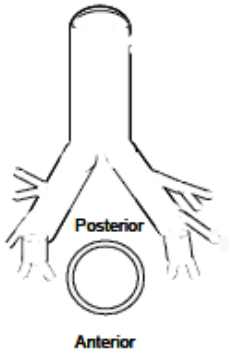
❑ **Check if waived surgery**

Please document tracheo-bronchial sites by marking diagrams accordingly:

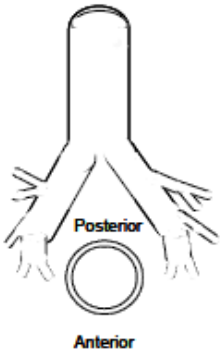
Clinical Papilloma



Biopsy Sites of Papilloma



Biopsy Sites of Adjacent Tissue



Please circle, using these criteria:
0= No involvement or obstruction
1= <1/3 involvement or obstruction
2= 1/3-2/3 involvement or obstruction
3= >2/3 involvement or obstruction

	Surface Area Involved (SA)				Extent of Lumen Obstruction (LO)			
Trachea	0	1	2	3	0	1	2	3
Carina	0	1	2	3	0	1	2	3
Bronchus	0	1	2	3	0	1	2	3
Trach Site	0	1	2	3	0	1	2	3
Sum of Scores	SA Scores:_____				LO Scores: _____			

B: Grand Total (Sum SA and LO scores) ☐ (between 0-24)

Calculation of Tracheobronchial Severity Score: $\frac{\text{Score A (from pg. 21) + Score B}}{\text{Number days since last surgery}}$ = ☐

Date last Surgery: ___/___/___ (MM DD YYYY)

Comments:

Signature:_____ Date _____
Person completing form

B. 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.

C. 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)

D. Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 Criteria for Evaluating Response in Solid Tumors

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

* As published in the European Journal of Cancer:

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

In addition, volumetric analysis will be explored by central review for response assessment.

E. Events of Clinical Interest Guidance Document

F. Quality of Life Questionnaires

G. Case Report Forms

H. Merck Drug Request Form

I. MK-3475 Pharmacy Manual

DFCI IRB Protocol #: 15-469

A Study of Anti-PD-1 therapy for HPV-associated Recurrent Respiratory Papilloma Patients with Laryngeal, Tracheal, and/or Pulmonary Involvement

APPENDIX J.

Dana-Farber/Harvard Cancer Center
Multi-Center Data and Safety Monitoring Plan

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1.0 INTRODUCTION

The Dana-Farber/Harvard Cancer Center Multi-Center Data and Safety Monitoring Plan (DF/HCC DSMP) outlines the procedures for conducting a DF/HCC Multi-Center research protocol. The DF/HCC DSMP should serve as a reference for any sites external to DF/HCC that will be participating in the research protocol.

1.1 Purpose

To establish standards that will ensure that a Dana-Farber/Harvard Cancer Center Multi-Center protocol will comply with Federal Regulations, Health Insurance Portability and Accountability Act (HIPAA) requirements and applicable DF/HCC Standard Operating Procedures.

1.2 Multi-Center Data and Safety Monitoring Plan Definitions

DF/HCC Multi-Center Protocol: A research protocol in which one or more outside institutions are collaborating with Dana-Farber/Harvard Cancer Center where a DF/HCC investigator is the sponsor. DF/HCC includes Dana-Farber/Partners Cancer Care (DF/PCC) Network Clinical Trial Affiliates.

Lead Institution: One of the Dana-Farber/Harvard Cancer Center consortium members (Dana-Farber Cancer Institute (DFCI), Massachusetts General Hospital (MGH), Beth Israel Deaconess Medical Center (BIDMC), Boston Children's Hospital (BCH), Brigham and Women's Hospital (BWH)) responsible for the coordination, development, submission, and approval of a protocol as well as its subsequent amendments per the DFCI IRB and applicable regulatory guidelines (CTEP, Food and Drug Administration (FDA), Office of Biotechnology Activities (OBA) etc.). The Lead Institution is typically the home of the DF/HCC Sponsor. The Lead Institution also typically serves as the Coordinating Center for the DF/HCC Multi-Center Protocol.

DF/HCC Sponsor: The person sponsoring the submitted Multi-Center protocol. Within DF/HCC, this person is the Overall Principal Investigator who takes responsibility for initiation, management and conduct of the protocol at all research locations. In applicable protocols, the DF/HCC Sponsor will serve as the single liaison with any regulatory agencies. The DF/HCC Sponsor has ultimate authority over the protocol and is responsible for the conduct of the study at DF/HCC and all Participating Institutions. In most cases the DF/HCC Sponsor is the same person as the DF/HCC Overall Principal Investigator; however, both roles can be filled by two different people.

Participating Institution: An institution that is outside the DF/HCC and DF/PCC consortium that is collaborating with DF/HCC on a protocol where the sponsor is a DF/HCC Investigator. The Participating Institution acknowledges the DF/HCC Sponsor as having the ultimate authority and responsibility for the overall conduct of the study.

Coordinating Center: The entity that provides administrative support to the DF/HCC Sponsor in order that he/she may fulfill the responsibilities outlined in the protocol document and DSMP, and as specified in applicable regulatory guidelines. In general, the Lead Institution is the Coordinating Center for the DF/HCC Multi-Center Protocol.

DF/HCC Office of Data Quality: A group within DF/HCC responsible for ensuring high-quality standards are used for data collection and the ongoing management of clinical trials, auditing, and data and safety monitoring.

2.0 GENERAL ROLES AND RESPONSIBILITIES

For DF/HCC Multi-Center Protocols, the DF/HCC Sponsor, the Coordinating Center, and the Participating Institutions are expected to adhere to the following general responsibilities:

2.1 DF/HCC Sponsor

The DF/HCC Sponsor, Sara Pai MD, PhD will accept responsibility for all aspects of conducting a DF/HCC Multi-Center protocol which includes but is not limited to:

- Oversee the coordination, development, submission, and approval of the protocol as well as subsequent amendments.
- Ensure that the investigators, study team members, and Participating Institutions are qualified and appropriately resourced to conduct the protocol.
- Include the Multi-Center Data and Safety Monitoring Plan as an appendix to the protocol.
- Ensure all Participating Institutions are using the correct version of the protocol.
- Ensure that each participating investigator and study team member receives adequate protocol training and/or a Site Initiation Visit prior to enrolling participants and throughout trial's conduct as needed.
- Ensure the protocol will be provided to each participating site in a language understandable to all applicable site personnel when English is not the primary language.
- Monitor progress and overall conduct of the study at all Participating Institutions.
- Ensure all DFCI Institutional Review Board (IRB), DF/HCC and other applicable (FDA) reporting requirements are met.
- Review data and maintain timely submission of data for study analysis.
- Act as the single liaison with FDA (investigator-held IND trials).
- Ensure compliance with all requirements as set forth in the Code of Federal Regulations, applicable DF/HCC requirements, HIPAA requirements, and the approved protocol.
- Commit to the provision that the protocol will not be rewritten or modified by anyone other than the DF/HCC Sponsor.
- Identify and qualify Participating Institutions and obtain accrual commitments prior to extending the protocol to that site.

- Monitor accrual and address Participating Institutions that are not meeting their accrual requirements.

2.2 Coordinating Center

The general responsibilities of the Coordinating Center may include but are not limited to:

- Assist in protocol development.
- Maintain FDA correspondence, as applicable.
- Review registration materials for eligibility and register participants from Participating Institutions.
- Distribute protocol and informed consent document updates to Participating Institutions as needed.
- Review and approve Participating Site informed consent forms
- Conduct and document initial and ongoing protocol training
- Oversee the data collection process from Participating Institutions.
- Maintain documentation and cumulative reports of Serious Adverse Event (SAE) reports and Deviations/Violations across all sites and provide to the DF/HCC Sponsor for timely review.
- Distribute serious adverse events reported to the DF/HCC Sponsor that fall under the DFCI IRB Adverse Event Reporting Policy to all Participating Institutions.
- Provide Participating Institutions with information regarding DF/HCC requirements that they will be expected to comply with.
- Carry out approved protocol monitoring plan either by on-site or remote monitoring.
- Maintain essential regulatory documents of all Participating Institutions which includes but is not limited to the following: local IRB approvals/notifications from all Participating Institutions, confirmation of Federalwide Assurances (FWAs) for all sites, all SAE submissions, Screening Logs for all sites, IRB approved consents for all sites, and protocol training documentation
- Conduct regular communications with all Participating Institutions (conference calls, emails, etc) and maintain documentation all relevant communications.

2.3 Participating Institution

Each Participating Institution is expected to comply with all applicable federal regulations and DF/HCC requirements, the protocol and HIPAA requirements.

The general responsibilities for each Participating Institution may include but are not limited to:

- Document the delegation of research specific activities to study personnel.
- Commit to the accrual of participants to the protocol.
- Submit protocol and/or amendments to their local IRB.
- Maintain regulatory files as per sponsor requirements.
- Provide the Coordinating Center with regulatory documents or source documents as requested.

- Participate in protocol training prior to enrolling participants and throughout the trial as required (i.e. teleconferences).
- Update Coordinating Center with research staff changes on a timely basis.
- Register participants through the Coordinating Center prior to beginning research related activities.
- Submit Adverse Event (SAE) reports to local IRB per local requirements and to the Coordinating Center, in accordance with DF/HCC or other sponsor requirements.
- Submit protocol deviations and violations to local IRB per local requirements and to the DF/HCC Sponsor in accordance with DF/HCC requirements.
- Order, store and dispense investigational agents and/or other protocol mandated drugs per federal guidelines and protocol requirements.
- Have office space, office equipment, and internet access that meet HIPAA standards.
- Participate in any quality assurance activities and meet with monitors or auditors at the conclusion of a visit to review findings.
- Promptly provide follow-up and/or corrective action plans for any monitoring queries or audit findings.

3.0 DF/HCC REQUIREMENTS FOR MULTI-CENTER PROTOCOLS

The following section will clarify DF/HCC Requirements and further detail the expectations for participating in a DF/HCC Multi-Center protocol.

3.1 Protocol Distribution

The Coordinating Center will distribute the final DFCI IRB approved protocol and any subsequent amended protocols to all Participating Institutions.

3.2 Protocol Revisions and Closures

The Participating Institutions will receive notification of protocol revisions and closures from the Coordinating Center. It is the individual Participating Institution's responsibility to notify its IRB of these revisions.

- **Non life-threatening revisions:** Participating Institutions will receive written notification of protocol revisions regarding non life-threatening events from the Coordinating Center. Non-life-threatening protocol revisions must be IRB approved and implemented within 90 days from receipt of the notification.

- **Revisions for life-threatening causes:** Participating Institutions will receive immediate notification from the Coordinating Center concerning protocol revisions required to protect lives with follow-up by fax, mail, e-mail, etc. Life-threatening protocol revisions will be implemented immediately followed by IRB request for approval.

- **Protocol closures and temporary holds:** Participating Institutions will receive notification of protocol closures and temporary holds from the Coordinating Center. Closures and holds will be effective immediately. In addition, the Coordinating Center, will update the Participating Institutions on an ongoing basis about protocol accrual data so that they will be aware of imminent protocol closures.

3.3 Informed Consent Requirements

The DF/HCC approved informed consent document will serve as a template for the informed consent for Participating Institutions. The Participating Institution consent form must follow the consent template as closely as possible and should adhere to specifications outlined in the DF/HCC Guidance Document on Model Consent Language for PI-Initiated Investigator Sponsored Multi-Center Trials. This document will be provided separately to each Participating Institution.

Participating Institutions are to send their version of the informed consent document and HIPAA authorization, if a separate document, to the Coordinating Center for review and approval prior to submission to their local IRB. The approved consent form must also be submitted to the Coordinating Center after approval by the local IRB for all consent versions.

The Principal Investigator (PI) at each Participating Institution will identify the physician members of the study team who will be obtaining consent and signing the consent form for therapeutic protocols. Participating institutions must follow the DF/HCC requirement that for all interventional drug, biologic, or device research only attending physicians may obtain initial informed consent and any re-consent that required a full revised consent form).

3.4 IRB Documentation

The following must be on file with the Coordinating Center:

- Initial approval letter of the Participating Institution's IRB.
- Copy of the Informed Consent Form(s) approved by the Participating Institution's IRB.
- Participating Institution's IRB approval for all amendments.
- Annual approval letters by the Participating Institution's IRB.

3.5 IRB Re-Approval

Verification of IRB re-approval from the Participating Institutions is required in order to continue research activities. There is no grace period for continuing approvals.

The Coordinating Center will not register participants if a re-approval letter is not received from the Participating Institution on or before the anniversary of the previous approval date.

3.6 Participant Confidentiality and Authorization Statement

In 1996, congress passed the first federal law covering the privacy of health information known as the Health Insurance Portability and Accountability Act (HIPPA). Any information, related to the physical or mental health of an individual is called Protected Health Information (PHI). HIPAA outlines how and under what circumstances PHI can be used or disclosed.

In order for covered entities to use or disclose protected health information during the course of a study, the study participant must sign an authorization statement. This authorization statement may or may not be separate from the informed consent document. The Coordinating Center, with the approval from the DFCI IRB, will provide a consent template, with information regarding authorization for the disclosure of protected health information.

The DF/HCC Sponsor will use all efforts to limit its use of protected health information in its trials. However, because of the nature of these trials, certain protected health information must be collected. DF/HCC has chosen to use authorizations, signed by the participant in the trial, rather than limited data sets with data use agreements.

3.6.1 DF/HCC Multi-Center Protocol Confidentiality

All documents, investigative reports, or information relating to the participant are strictly confidential. Whenever reasonably feasible, any participant specific reports (i.e. Pathology Reports, MRI Reports, Operative Reports, etc.) submitted to the Coordinating Center should be de-identified. It is recommended that the assigned DF/HCC QACT case number (as described below) be used for all participant specific documents. Participant initials may be included or retained for cross verification of identification.

3.7 DF/HCC Multi-Center Protocol Registration Policy

All participants must be registered with DF/HCC prior to conducting any research-related procedures

3.7.1 Participant Registration

Please refer to protocol Section 6.0: Registration Procedures

3.7.2 Initiation of Therapy

Participants must be registered with the DF/HCC ODQ before receiving treatment. Treatment may not be initiated until the Participating Institution receives confirmation of the participant's registration from the Coordinating Center. The DF/HCC Sponsor and DFCI IRB must be notified of any violations to this policy.

3.7.3 Eligibility Exceptions

The DF/HCC ODQ will make no exceptions to the eligibility requirements for a protocol without DFCI IRB approval. The DF/HCC ODQ requires each institution to fully comply with this requirement.

3.8 DF/HCC Protocol Case Number

At the time of registration, the following identifiers are required for all subjects: initials, date of birth, gender, race and ethnicity. Once eligibility has been established and the participant successfully registered, the participant is assigned a unique protocol case number. Participating Institutions should submit all de-identified subsequent communication and documents to the Coordinating Center, using this case number to identify the subject.

3.8.1 Protocol Deviations, Exceptions and Violations

Federal Regulations require an IRB to review proposed changes in a research activity to ensure that researchers do not initiate changes in approved research without IRB review and approval, except when necessary to eliminate apparent immediate hazards to the participant. DF/HCC requires all departures from the defined procedures set forth in the IRB approved protocol to be reported to the DF/HCC Sponsor, who in turn is responsible for reporting to the DFCI IRB.

For reporting purposes, DF/HCC uses the terms "violation", "deviation" and "exception" to describe departures from a protocol. All Participating Institutions must adhere to these requirements for reporting to the DF/HCC Sponsor and will follow their institutional policy for reporting to their local IRB.

3.8.2 Definitions

Protocol Deviation: Any departure from the defined procedures set forth in the IRB-approved protocol which is prospectively approved prior to its implementation.

Protocol Exception: Any protocol deviation that relates to the eligibility criteria, e.g. enrollment of a participant who does not meet all inclusion/exclusion criteria.

Protocol Violation: Any protocol deviation that was not prospectively approved by the IRB prior to its initiation or implementation.

3.8.3 Reporting Procedures

DF/HCC Sponsor: is responsible for ensuring that clear documentation is available in the medical record and/or regulatory documents to describe all protocol exceptions, deviations and violations. The DF/HCC Sponsor will also be responsible for ensuring that all protocol violations/deviations are promptly reported per DFCI IRB guidelines.

Participating Institutions: Protocol deviations require prospective approval from the DFCI IRB. The Participating Institution must submit the deviation request to the Coordinating Center who will then submit the deviation request to the DFCI IRB. Upon DFCI IRB approval the deviation is submitted to the Participating Institution IRB, per institutional policy. A copy of the Participating Institution's IRB report and determination will be forwarded to the Coordinating Center within 10 business days after the original submission.

All protocol violations must be sent to the Coordinating Center in a timely manner.

Coordinating Center: Upon receipt of the violation/deviation report from the Participating Institution, the Coordinating Center will submit the report to the DF/HCC Sponsor for review. Subsequently, the Participating Institution's IRB violation/deviation report will be submitted to the DFCI IRB for review per DFCI IRB reporting guidelines. DF/HCC will forward all violation reports to CTEP via an internal DF/HCC process, as applicable.

3.9 Safety Assessments and Toxicity Monitoring

The study teams at all participating institutions are responsible for protecting the safety, rights and well-being of study participants. Recording and reporting of adverse events that occur during the course of a study help ensure the continuing safety of study participants.

All participants receiving investigational agents and/or other protocol mandated treatment will be evaluated for safety. The safety parameters include all laboratory tests and hematological abnormalities, physical examination findings, and spontaneous reports of adverse events reported by participants. All toxicities encountered during the study will be evaluated according to the NCI criteria specified in the protocol. Life-threatening toxicities must be reported immediately to the DF/HCC Sponsor via the Coordinating Center.

Additional safety assessments and toxicity monitoring will be outlined in the protocol.

3.9.1 Guidelines for Reporting Serious Adverse Events

Guidelines for reporting Adverse Events (AEs) and Serious Adverse Events (SAEs) are detailed in protocol section 11.0: Adverse Event Reporting Requirement.

Participating Institutions must report the SAEs to the DF/HCC Sponsor and the Coordinating Center following the DFCI IRB Adverse Event Reporting Policy.

The Coordinating Center will maintain documentation of all Participating Institution Adverse Event reports and be responsible for communicating to all participating investigators, any observations reportable under the DFCI IRB Reporting Requirements. Participating Institutions will review and submit to their IRB according to their institutional policies and procedures

3.9.2 Guidelines for Processing IND Safety Reports

The DF/HCC Sponsor will review all IND Safety Reports and ensure that all IND Safety Reports are distributed to the Participating Institutions. Participating Institutions will review and submit to their IRB according to their institutional policies and procedures.

3.10 Data Management

The DF/HCC ODQ develops case report forms (CRF/eCRFs), for use with the protocol. These forms are designed to collect data for each study. The DF/HCC ODQ provides a web based training for eCRF users.

3.10.1 Data Forms Review

Data submissions are monitored for timeliness and completeness of submission. Participating Institutions are notified of their data submission delinquencies in accordance with the following:

Incomplete or Questionable Data
If study forms are received with missing or questionable data, the submitting institution will receive a written or electronic query from the DF/HCC ODQ Data Analyst, Coordinating Center or designee. Responses to all queries should be completed and submitted within 14 calendar days. Responses may be returned on the written query or on an amended paper case report form, or in the case of electronic queries, within the electronic data capture (eDC) system. In the case of a written query for data submitted on a paper case report form, the query must be attached to the specific data being re-submitted in response.

Missing Forms
If study forms are not submitted on schedule, the Participating Institution will receive a Missing Form Report from the Coordinating Center noting the missing forms. These reports are compiled by the DF/HCC ODQ and distributed on a monthly basis.

4.0 REQUISITIONING INVESTIGATIONAL DRUG

The ordering of investigational agent is specified in the protocol section 15.2: Ordering Investigational Product.

Participating Institutions should order their own agent regardless of the supplier.

If the agent is commercially available, check with the local Director of Pharmacy and/or the Research Pharmacy to ensure that the agent is in stock. If the agent is not stocked, ensure that the agent can be ordered once the protocol is approved by the local IRB.

If the agent is investigational, ensure that the pharmacy will be able to receive and store the agent according to state and federal requirements. The local IRB should be kept informed of who will supply the agent (i.e., NCI or a pharmaceutical company) so that any regulatory responsibilities can be met in a timely fashion.

5.0 MONITORING: QUALITY CONTROL

The quality control process for a clinical trial requires verification of protocol compliance and data accuracy. The Coordinating Center, with the aid of the ODQ provides quality control oversight for the protocol.

5.1 Ongoing Monitoring of Protocol Compliance

All Participating Institution will be monitored and are subject to on-site as well as remote monitoring conducted by the Coordinating Center. Participating Institutions will be required to submit relevant participant source documents to the Coordinating Center for monitoring.

The Coordinating Center will implement ongoing monitoring activities to ensure that Participating Institutions are complying with regulatory and protocol requirements, data quality, and participant safety. Monitoring will occur before the clinical phase of the protocol begins, continue during protocol performance and through study completion. Monitoring practices include but are not limited to; source verification, review and analysis of the following: eligibility requirements of all participants, informed consent procedures, adverse events and all associated documentation, study drug administration/treatment, regulatory files, protocol departures, pharmacy records, response assessments, and data management.

All DF/HCC sites and Participating Institutions will undergo on-site monitoring by the Coordinating Center within 3 months of enrollment of the first patient at each site. Combination on-site and remote monitoring will occur every 4-6 months thereafter with at least 1 on-site visit every 12 months while the site is actively accruing and treating patients.

Once all site participants are off treatment and have completed the post-treatment Safety Follow-Up Visit, the follow-up monitoring schedule will be revised to a combination of remote and on-site monitoring conducted every 6 months, with at least one on-site visit

every 18 months for confirmation of long term follow-up data. Once all subjects have completed follow-up at a given site, monitoring will be limited to annual, remote review of overall survival data, confirm off-study data entry and to verify regulatory review.

Additional monitoring may be conducted for cause or at the discretion of the Principal Investigator.

For remote monitoring visits, Participating Institutions will be asked to provide remote electronic medical record access to the monitor or will be required to forward de-identified copies of participants' medical record and source documents to the Coordinating Center to aid in source data verification. The participants and CRFs to be reviewed at the visit will be communicated at least 2 weeks in advance of the scheduled monitoring visit. Source documentation can be provided to the Coordinating Center via an encrypted memory stick or via a secure file transfer system. During remote monitoring visits, the Site Specific File will be reviewed in lieu of the site regulatory binder.

On-Site Monitoring will be scheduled several weeks in advance and will be conducted over a 2-3 day period. During an on-site monitoring visit 2-4 participants will be monitored. Source documentation verification (SDV) will be conducted by having access to participants' complete medical record and source documents. Participating Institutions will be expected to coordinate the necessary resources for the monitor, including a desk, access to all participant medical and research records (electronic and hard copy), the regulatory binders and access to a photocopier. The Participating Institution will also be asked to assist in scheduling a pharmacy visit and a brief exit interview on the final day of the visit with the Study Coordinator and the Site investigator.

All Participating Institutions will be required to participate in monthly Coordinating Center initiated teleconferences. Once all participants have completed treatment, teleconferences will be scheduled as needed.

5.2 Monitoring Reports

The DF/HCC Sponsor will review all monitoring reports for on-site and remote monitoring of Participating Institutions to ensure protocol compliance. The DF/HCC Sponsor may increase the monitoring activities at Participating Institutions that are unable to comply with the protocol, DF/HCC Sponsor requirements or federal and local regulations. Participating Institutions may also be subject to an audit as determined by the DF/HCC Sponsor.

5.3 Accrual Monitoring

Prior to extending a protocol to an external site, the DF/HCC Sponsor will establish accrual requirements for each participating institution. For Phase II studies, sites are expected to accrue at least 3 participants annually, with the exception of rare disease groups. Accrual will be monitored for each participating institution by the DF/HCC

Sponsor or designee. Sites that are not meeting their accrual expectations may be subject to termination.

6.0 AUDITING: QUALITY ASSURANCE

Auditing is a method of Quality Assurance. Its main focus is to measure whether standards and procedures were followed. Auditing is the systematic and independent examination of all trial related activities and documents. Audits determine if evaluated activities were appropriately conducted and whether data was generated, recorded and analyzed, and accurately reported per the protocol, Standard Operating Procedures (SOPs), and the Code of Federal Regulations (CFR).

6.1 Audit Plan: NCI Sponsored Trials

Not applicable

6.2 Audit Plan: DF/HCC Sponsored Trials

One on-site audit will be scheduled by the ODQ, assuming at least three participants have been treated on protocol at the site. Approximately 3-4 participants would be audited at the site over a 2 day period. If violations which impact participant safety or the integrity of the study are found, more participant records may be audited.

6.3 Audit Notification

It is the Participating Institution's responsibility to notify the Coordinating Center of all scheduled audit dates (internal or NCI) and re-audit dates (if applicable), which involve this protocol. All institutions will forward a copy of final audit and/or re-audit reports and corrective action plans (if applicable) to the Coordinating Center, within 12 weeks after the audit date.

6.4 Audit Reports

The DF/HCC Sponsor will review all final audit reports and corrective action plans if applicable. The Coordinating Center, must forward these reports to the DF/HCC ODQ per DF/HCC policy for review by the DF/HCC Audit Committee. Based upon the audit assessments the DF/HCC Audit Committee could accept or conditionally accept the audit rating and final report. Conditional approval could require the DF/HCC Sponsor to implement recommendations or require further follow-up. For unacceptable audits, the DF/HCC Audit Committee would forward the final audit report and corrective action plan to the DFCI IRB as applicable.

6.5 Participating Institution Performance

The DF/HCC Sponsor and the DFCI IRB is charged with considering the totality of an institution's performance in considering institutional participation in the protocol.

6.5.1 Corrective Actions

Participating Institutions that fail to meet the performance goals of accrual, submission of timely and accurate data, adherence to protocol requirements, and compliance with state and federal regulations, may be recommended for a six-month probation period. Such institutions must respond with a corrective action plan and must demonstrate during the probation period that deficiencies have been corrected, as evidenced by the improved performance measures. Participating Institutions that fail to demonstrate significant improvement will be considered by the DF/HCC Sponsor for revocation of participation. A DF/HCC Sponsor and/or the DFCI IRB may terminate a site's participation if it is determined that a site is not fulfilling its responsibilities as described above.