Abbreviated Title: M7824 for RRP
NIH Protocol #: 19C0002
NCT #: NCT03707587
Version Date: 12/1/2020

Title: A Phase II Study of M7824 in Subjects with Recurrent Respiratory Papillomatosis

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Investigational Agent:

Drug Name:	M7824
IND Number:	138835
Sponsor:	Center for Cancer Research
Manufacturer:	EMD Serono

Commercial Agents: None

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PRÉCIS

Background

- Recurrent respiratory papillomatosis (RRP) is a rare papillomatous disease of the aerodigestive tract that is caused by the Human Papilloma Virus (HPV).
- RRP can progress to cause airway compromise, fatal pulmonary lesions, and invasive cancers.
- There is no effective systemic therapy for RRP. Patients typically require repeated interventional procedures for disease control.
- A recently completed phase II clinical trial investigating avelumab in subjects with aggressive RRP demonstrated an acceptable safety profile from avelumab and a high rate of partial responses.
- RRP is characterized by frequent expression of PD-L1 and TGF-beta in the tumor microenvironment.
- This clinical trial will evaluate the activity of M7824, a novel bifunctional fusion protein composed of a fully human IgG1 monoclonal antibody against human PD-L1 (avelumab) fused, via a flexible glycine-serine linker, to the soluble extracellular domain of human TGF-β receptor II (TGF-βRII), which functions as a TGF-β "trap." This drug was selected for its demonstrated activity in a variety of cancers and for its acceptable safety profile.

Objective

- Determine the complete response rate for M7824 in the treatment of patients with RRP.

Eligibility

- Histologically confirmed diagnosis of RRP.
- One of the following:
    - A Derkay anatomic score of 10 or greater and a history of two or more endoscopic interventions in the last 12 months for control of RRP.
    - Pulmonary RRP with pulmonary disease that is measurable by computed tomography scan.
    - Tracheal involvement with RRP that has required either two or more endoscopic interventions in the last 12 months or a tracheostomy.
- Age 18 years or greater.
- Eastern Oncology Cooperative Group Performance Score of 0 or 1.

Design

- This is a phase II clinical trial with two cohorts that will enroll simultaneously.
- Cohort 1 will consist of subjects who have not been treated previously with an immune checkpoint inhibitor. Cohort 2 will consist of subjects whose disease has been treated previously with and refractory to an immune checkpoint inhibitor. Each cohort will have a Simon optimal two-stage design with initial enrollment of 12 patients and expansion to 21

Robbins Y, *et al. J Immunother Cancer* 2021; 9:e003113. doi: 10.1136/jitc-2021-003113

patients if one or more complete response(s) is/are observed in the initial patients. With amendment D, dated 7/24/2019, cohort 2 will be closed to further enrollment.

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STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; an IRB determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

1 INTRODUCTION

1.1 STUDY OBJECTIVES

1.1.1 Primary Objective

- To determine the complete response rate for M7824 in the treatment of patients with recurrent respiratory papillomatosis (RRP).

1.1.2 Secondary Objective

- Determine the partial response rate for M7824.
- Determine safety of M7824 in patients with RRP.

1.1.3 Exploratory Objectives

- Determine the effect of treatment with M7824 on Derkay and Voice Handicap Index-10 scores.
- PD-L1 and/or TGF-β expression as a potential biomarker of response.
- Determine the duration of clinical responses to M7824.
- HPV type as a potential biomarker of response.
- Induction of HPV-specific T cell responses.
- Clearance of HPV infection from normal appearing mucosa.

1.2 BACKGROUND AND RATIONALE

1.2.1 Recurrent respiratory papillomatosis (RRP)

RRP is a rare but difficult-to-treat and sometimes fatal neoplastic disease of the aerodigestive tract. RRP is caused by infection with human papillomavirus (HPV) type 6 or 11, or more rarely type 16 (1). Approximately 1,500 new cases of RRP are diagnosed each year in the United States

(2). RRP is classified based on age of onset as juvenile or adult. Juvenile-onset disease has an incidence of 4/100,000 and tends to have an aggressive clinical course. Adult-onset RRP has an incidence of 2-3/100,000 and tends to have a more indolent clinical course. RRP morbidity and mortality results from papilloma mass effects on the vocal cords, airways, or lungs. This may cause voice changes, stridor, airway occlusion, loss of lung volume, and/or pneumonia (3). Repeated procedures are required to debulk and monitor the disease, which exposes patients to anesthetic and surgical risk, and emotional distress. It is estimated that the economic cost of RRP is $150M in the United States each year (2). Although rare (one to three percent of cases) RRP can transform into invasive squamous cell carcinoma (4). Subsequent mortality is based upon the clinical stage of the malignancy at the time of diagnosis.

There is no cure for RRP. The mainstay of treatment is endoscopic debulking with ablation or excision of papillomatous lesions. Surgical principles dictate that, to minimize morbidity from treatment, papillomatous disease but not normal appearing epithelium is removed. It is thought that latent HPV viral particles persist in an inactive state in the clinically-normal mucosa and subsequently become reactivated leading to RRP recurrence (5). Patients with juvenile-onset RRP require on average 20 surgeries over their lifetime to control their disease (6). Patients with adult-onset RRP generally require fewer interventions; nonetheless greater than 50% will require 5 or more procedures to control symptoms (7). Adjuvant systemic therapies have been tested in clinical trials, including systemic interferon-α and local injection of anti-viral and antiangiogenic agents (5). Study results have been inconsistent, and no single adjuvant approach has been widely adopted or accepted as the standard of care.

RRP is caused by HPV infection. HPV infections are common, but most individuals clear the virus without manifesting papillomas, dysplasia, or invasive cancers (8). Why some immunocompetent individuals are unable to eliminate the virus and therefore develop papillomatosis is not understood. Local therapies fail to eradicate the disease apparently due to chronic persistence of latent virus in normal appearing mucosa. This notion is supported by a study demonstrating the presence of HPV DNA in the clinically healthy mucosa of patients with RRP (9, 10). Efforts to study systemic immunotherapy for RRP have been limited. Adjuvant IFN-α after papilloma treatment was shown to increase short-term time to recurrence but did not demonstrate long-term benefit (11).

Programmed death ligand 1 (PD-L1) expression on tumor cells has been associated strongly with poor prognosis in a variety of human cancers. (12) In recent years, a number of agents targeting the programmed death 1 (PD-1)/PD-L1 pathway have received regulatory approval, demonstrating impressive durations of response for multiple tumor types, including melanoma, non-small cell lung cancer, renal cell cancer, and head and neck cancer (13-17). Notably, atezolizumab, durvalumab and avelumab are all anti–PD-L1 antibodies with proven efficacy and regulatory approval. Study of a small number of RRP samples by our group has shown PD-L1 expression by inflammatory mononuclear cells and by papilloma epithelial cells (18). In response to this data, we recently completed a phase II study investigating the role of avelumab in patients with aggressive RRP. We found that while the majority of patients demonstrated partial responses to single agent avelumab (**Figure 1**), no complete responses were achieved. Toxicities were generally mild and comparable to previous safety data with avelumab.

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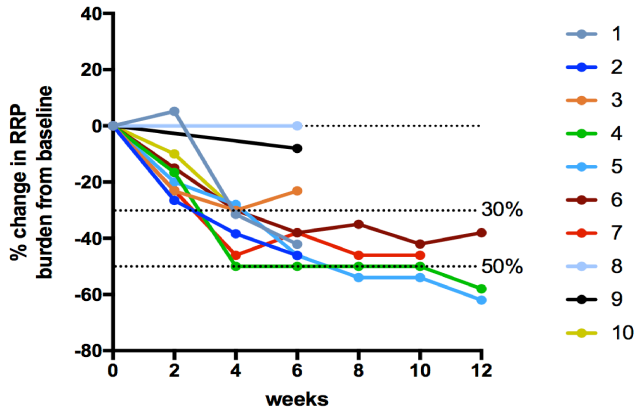

Figure 1: *Clinical responses to phase II study of avelumab in patients with aggressive RRP*

1.2.2 TGF-β/ TGFβR1 signaling pathway

In an effort to increase the rate of response to these therapies, clinical trials are evaluating anti–PD-1/PD-L1 agents in combination with other immunotherapies (19). Importantly, combined inhibition of PD-L1 and TGF-β is a promising therapeutic strategy because these key pathways have independent immunosuppressive functions.

Transforming growth factor β (TGF-β) is a pleiotropic cytokine. In patients with cancer, TGF-β is associated with malignant progression, evasion of immune surveillance, invasion, and metastasis (20, 21). TGF-β Receptor 1 (TGFβR1*)* pathway signalling and overexpression have also been found to be significantly associated with HPV+ cancers (22). Based on two genome wide association studies (GWAS) which compared patients with upper aero-digestive (n= 2091) and cervical cancers (n=617) to cancer free patients (8,334 and 512 respectively), an integrative computational analysis (including single-gene, gene-interconnectivity, protein–protein interaction, gene expression, and pathway analysis) looked to identify immune genes and pathways significantly associated with HPV+ cervical and oropharyngeal cancer. They found that TGFβR1 expression and downstream signalling was significantly increased in HPV+ cervical cancer and head and neck cancers (22). Similarly, TGF-β has been shown to be significantly expressed in the microenvironment of RRP specimens (23).

The direct effects of TGF-β on T cells include decreases in perforin, granzymes, interferon gamma, Fas ligand, and natural killer group 2D (NKG2D). It can also decrease NKG2D and major histocompatibility complex (MHC) class I polypeptide sequence A (MICA) in natural killer (NK) cells (24). Elevated levels of TGF-β have been found to correlate with poor outcomes in many different human cancers (25). Antibodies (e.g., fresolimumab) and small-molecule inhibitors (e.g., galunisertib) targeting the TGF-β pathway have entered clinical development, where they have shown promise in hepatocellular carcinoma, pancreatic cancer, and melanoma (26).

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1.2.3 M7824

M7824 is a novel bifunctional fusion protein composed of a fully human IgG1 monoclonal antibody against human PD-L1 fused, via a flexible glycine-serine linker, to the soluble extracellular domain of human TGF-β receptor II (TGF-βRII), which functions as a TGF-β "trap." The anti-D-L1 moiety of M7824 is based on avelumab (MSB0010718C), which is currently in Phase III clinical trials in multiple tumor types and was recently FDA approved for metastatic Merkel cell Carcinoma and urothelial carcinoma (27, 28). Preclinical studies have shown its ability to simultaneously bind PD-L1 and TGF-β, as well as appropriately block PD-L1 signaling and TGF-β signaling in vitro. M7824 was shown to have better antitumor efficacy than anti-PD-L1 or TGF-β trap control (a mutated antibody that doesn't bind to PD-L1, linked with the TGF-β trap) in both MC38 and EMT-6 tumor models in both wild-type mice and B cell deficient mice. Because M7824 is very immunogenic in mice, due to the fully human antibody and its immunostimulatory mechanism of action, host anti-drug antibodies preclude continued dosing. In an orthotopic EMT-6 breast cancer model using B cell-deficient Jh mice M7824 showed much better activity than either anti-PD-L1 antibody alone or TGF-β trap control (**Figure 2**)

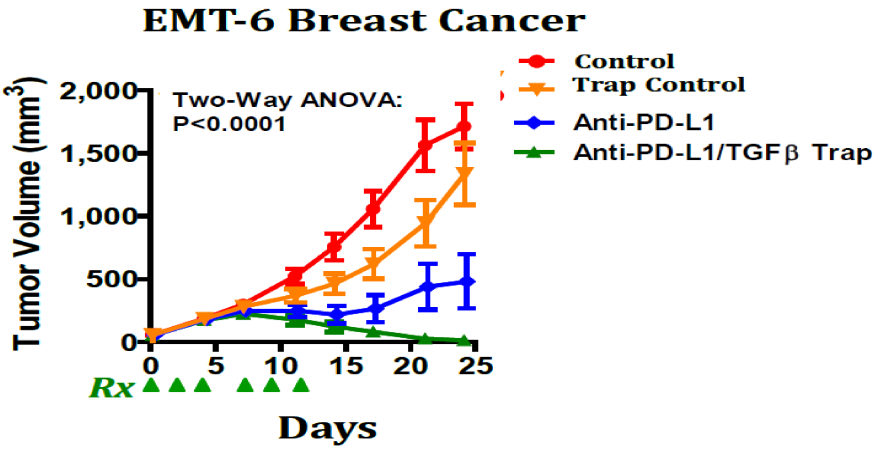

Figure 2: *Preclinical studies using B cell-deficient Jh mice with subcutaneous EMT-6 breast cancer tumors showing significantly reduced tumor volume with M7824 (anti-PD-L1/TGFβ) compared with either anti-PDL1 antibody or TGF-β trap alone.*

At tumor re-challenge, 13/13 mice previously cured with M7824 treatment had complete protection. Furthermore, M7824 therapy extended survival in a dose dependent manner. Similar results were also observed in the MC38 colorectal carcinoma model. Furthermore, depletion studies in MC38 model demonstrated that both CD8+ cytotoxic T cells and NK cells are required for tumor rejection (**Figure 3**).

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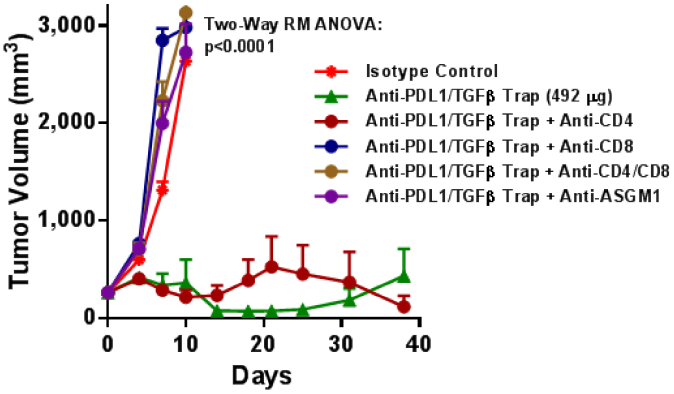

Figure 3: *Antibody-based, selective depletion of immune effector cell subsets showed that both CD8+ cytotoxic T cells and NK cells are required for tumor rejection with M7824 (Anti-PD-L1/TGFβ Trap) in MC38 model.*

In *in vivo* studies, not only did M7824 decrease TGF-β in the serum and bind PDL1 within the tumor, it also substantially increased CD8+ T-cell and NK cell infiltration within the tumor, while decreasing myeloid-derived suppressor cell (MDSC) infiltration, compared with an anti–PD-L1 antibody control.

Based on these preclinical data, a Phase I 3+3 dose-escalation study was completed to evaluate the pharmacokinetics (PK), safety, tolerability, and biological and clinical activity of M7824 in patients with advanced solid tumors (NCT02517398).

Sixteen heavily pretreated patients received M7824 at 1, 3, 10, or 20 mg/kg once-every-2-weeks. M7824 was shown to saturate peripheral PD-L1 at doses ≥ 3 mg/kg and sequester plasma TGF-β1, -β2, and -β3 (**Figure 4**) throughout the dosing period at ≥1 mg/kg. The only DLT observed was colitis with associated anemia (20 mg/kg). No MTD was reached. Grade 3 treatment-related adverse events occurred in 3 patients (skin infection secondary to localized bullous pemphigoid (3 mg/kg), asymptomatic lipase increase (20 mg/kg), and colitis (20 mg/kg) with associated anemia). These toxicities are on par with other PD-1/PD-L1 inhibitors. The only added toxicity seen over traditional PD-1/PD-L1 inhibitors was the occurrence of keratoacanthomas which have been described previously with TGFβ inhibitors (29). Keratoacanthomas appear in approximately 10% of treated patients, but usually resolve with discontinuation of therapy. There were no treatment-related grade 4–5 events. Based upon this safety data the decision was made to treat subsequent patient cohorts with a dose of 1,200 mg IV once every 2 weeks. This dose has been used in several phase Ib expansion cohorts treating more than 500 patients. This dose has been recommended for all phase II trials using M7824.

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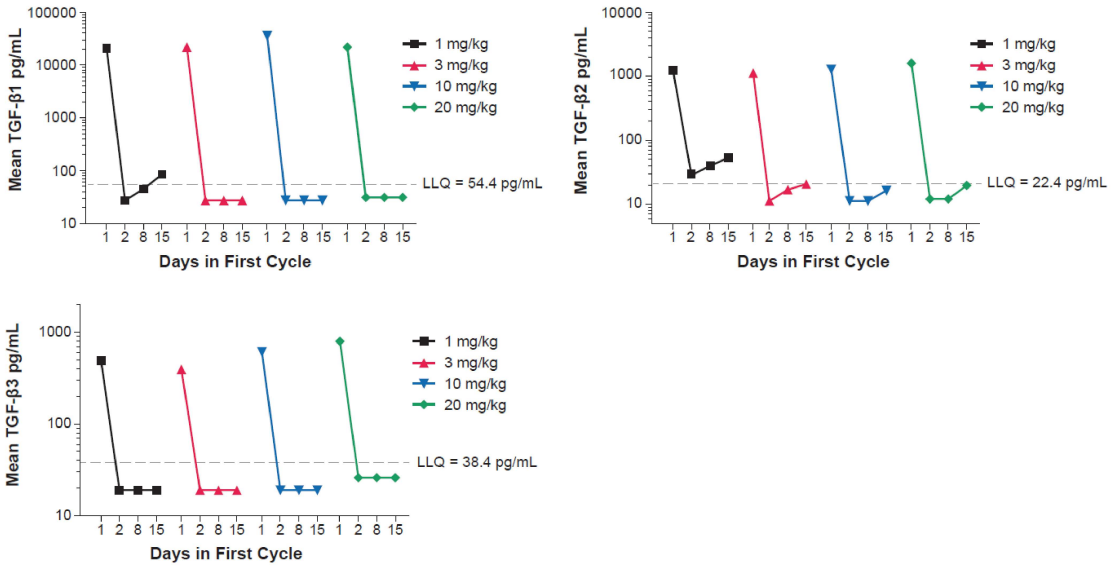

Figure 4: Total TGF-β1, -β2, and -β3 plasma concentrations following intravenous administration of M7824.

In addition, in the ongoing Phase I study of M7824 (NCT02517398), substantial clinical evidence has been seen in 4 of 9 subjects (44%) with HPV-associated malignancies, including 2 of 5 patients (40%) with metastatic cervical cancer, 1 of 2 patients (50%) with metastatic anal cancer and 1 of 2 patients (50%) with metastatic P16+ head and neck cancer have had substantial clinical benefit.

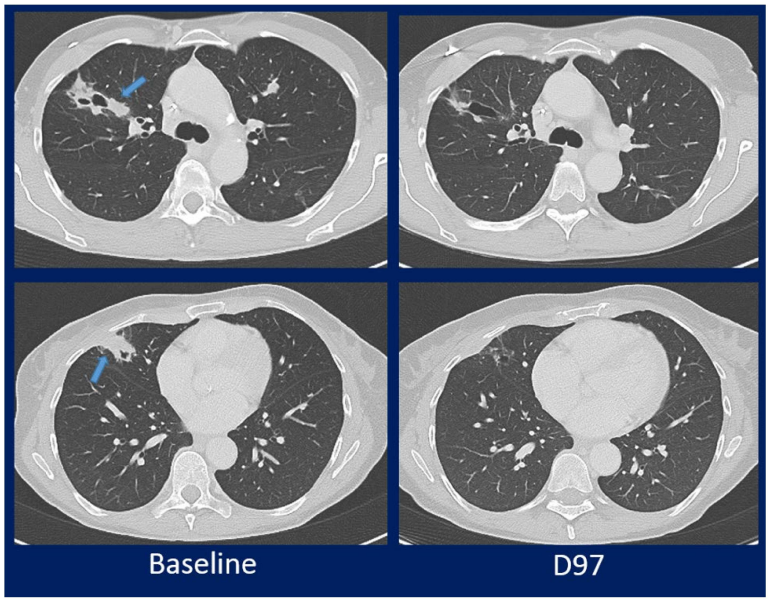

Figure 5: This 56-year-old woman with initially locally advanced cervical cancer status post (s/p) cisplatin/RT developed metastases to lung within 3 months of initial treatment. Then went on to receive topotecan/taxol plus bevacizumab and was enrolled on phase I of M7824 with enlarging right-sided lung masses (arrows in left side of figure). She received 2 doses of M7824 at 20 mg/kg but then developed colitis necessitating drug discontinuation. Despite this her restaging scan at 12 weeks showed marked reduction in disease volume (right side of figure).

This includes a subject with metastatic cervical cancer with a 25% reduction (by long axis measurement) in her disease at 3 months (Figure 5), a subject with metastatic P16+ head and neck cancer with an unconfirmed partial response 6 weeks after starting treatment, a patient with metastatic anal cancer with normalization of tumor markers and an ongoing durable partial response 9 months after starting treatment and a patient with metastatic cervical cancer with normalization of tumor markers and an ongoing durable complete response for more than a year.

This early data from a small cohort of subjects with HPV-associated malignancies in this phase 1 trial of M7824 suggests that this agent, which targets both PD-L1 and TGF-β pathways, may produce responses at a higher rate as compared with other single agent PD-1/PD-L1 inhibitors. Here, we aim to assess the clinical response rate following treatment with M7824 in subjects with aggressive RRP.

2 ELIGIBILITY ASSESSMENT AND ENROLLMENT

2.1 ELIGIBILITY CRITERIA

2.1.1 Inclusion Criteria

2.1.1.1 RRP criteria

- Histological diagnosis of RRP confirmed by pathology report from a CLIA-certified laboratory.
- One of the following:
    - A Derkay anatomic score of 10 or greater (See Section 13.4) and a history of two or more endoscopic interventions in the last 12 months for control of RRP.
    - Pulmonary RRP with pulmonary disease that is measurable by computed tomography scan and evaluated by RECIST Criteria.
    - Tracheal involvement with RRP that has required either two or more endoscopic interventions in the last 12 months or a tracheostomy.

2.1.1.2 Greater than or equal to 18 years of age.

2.1.1.3 Able to understand and sign the Informed Consent Document.

2.1.1.4 Clinical performance status of ECOG 0 or1. See section 13.1

2.1.1.5 Willing to undergo endoscopic evaluation with biopsies in compliance with this protocol.

2.1.1.6 No systemic therapy for RRP for at least 3 half-lives of the prior drug(s).

2.1.1.7 Screening laboratory values must meet the following criteria and should be obtained within 14 days prior to first dose:

- WBC > 2000/μL

- Neutrophils > 1000/μL
- Platelets > 75 x10^3/μL
- Hemoglobin > 9.0 g/dL
- Serum Creatinine < 1.5 x ULN OR eGFR > 30 mL/min (measured or calculated using the MDRD equation).
- AST/ALT ≤ 2.5 x ULN
- Total Bilirubin ≤ 1.5 x ULN
- PT/INR and PTT ≤ ULN

2.1.1.8 Sexually active subjects (men and women) of reproductive potential must agree to use two methods of contraception: one highly effective and one other effective method throughout M7824 treatment and for at least 120 days after M7824 treatment. Highly Effective Methods are defined as: Intrauterine device (IUD), hormonal (birth control pills, injections, implants), tubal ligation and partner's vasectomy; Other Effective Methods are defined as: latex condom, diaphragm and cervical cap.

2.1.1.9 Seronegative for HIV antibody. The experimental treatment being evaluated in this protocol depends on an intact immune system. Patients who are HIV seropositive can have decreased immune function and thus are likely less responsive to the experimental treatment.

2.1.1.10 Seronegative for hepatitis B antigen, positive hepatitis B tests can be further evaluated by confirmatory tests (Hep B DNA Quant, HBV Viral Load), and if confirmatory tests are negative, the patient can be enrolled.

2.1.1.11 Seronegative for hepatitis C antibody unless antigen negative. If hepatitis C antibody test is positive, then patients must be tested for the presence of antigen by Hep C RNA Quant, HCV Viral Load and be HCV RNA negative.

2.1.2 Exclusion criteria

2.1.2.1 Any severe acute or chronic medical or psychiatric conditions including recent (within the past year) or active suicidal ideation or behavior, liver disease, lung disease (with the exception of what is specified in inclusion criteria in section **2.1.1.1**) , or laboratory abnormalities that, in the opinion of the investigators, may increase the risk associated with study participation or study drug administration, impair the ability of the subject to receive protocol therapy, or interfere with the interpretation of study results and in the judgment of the investigator, would make the patient inappropriate for entry into this study. Patients with mild to moderate asthma or chronic obstructive pulmonary disease (COPD) well controlled with oral or inhaled medications are permitted to enroll.

2.1.2.2 Subjects with active, known or suspected autoimmune disease. Subjects with vitiligo, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, or psoriasis not requiring systemic treatment, are permitted to enroll.

2.1.2.3 Subjects with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of study drug administration. Inhaled, topical intranasal or intro-ocular steroids,

and adrenal replacement doses <10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease.

2.1.2.4 Prior organ transplantation, including allogeneic stem cell transplantation.

2.1.2.5 Patients who are receiving any other investigational agents

2.1.2.6 Pregnant or breast feeding. Women of childbearing potential must have a negative pregnancy test at screening. Women of childbearing potential include women who have experienced menarche and who have not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or are not postmenopausal. Post-menopause is defined as amenorrhea ≥12 consecutive months. Note: women who have been amenorrheic for 12 or more months are still considered to be of childbearing potential if the amenorrhea is possibly due to prior chemotherapy, anti-estrogens, ovarian suppression or any other reversible reason.

2.1.2.7 History of allergy to study drug components.

2.1.2.8 History of severe hypersensitivity reaction to any monoclonal antibody (Grade ≥ 3 NCI-CTCAE v 5.0), any history of anaphylaxis, or uncontrolled asthma (that is, 3 or more features of partially controlled asthma).

2.1.2.9 Clinically significant (i.e., active) cardiovascular disease: cerebral vascular accident/stroke (< 6 months prior to enrollment), myocardial infarction (< 6 months prior to enrollment), unstable angina, congestive heart failure (≥ New York Heart Association Classification Class II), or serious cardiac arrhythmia requiring medication.

2.1.2.10 Persisting toxicity related to prior therapy of Grade >1 NCI-CTCAE v 5.0; however, alopecia, sensory neuropathy Grade ≤ 2 or other Grade ≤ 2 AEs not constituting a safety risk based on investigator's judgment are acceptable.

2.1.2.11 Known alcohol or drug abuse.

2.1.2.12 Vaccination within 4 weeks of the first dose of M7824 and 4 weeks after the last dose of M7824 are prohibited.

2.1.2.13 HPV vaccination within one year of the first dose of M7824

2.1.2.14 With amendment D, patients that received prior PD-1 based immunotherapy will be excluded.

2.2 SCREENING EVALUATION

Study eligibility is based on meeting all of the study inclusion criteria and none of the exclusion criteria at screening before study treatment administration. Screening evaluations may be performed as part of an NIH Screening protocol. This does not include the baseline correlative studies that will only be performed after the patient has signed the consent form for this protocol.

2.2.1 Within 14 days prior to subject enrollment, unless otherwise indicated below:

2.2.1.1 Complete history and physical examination, including ECOG status, weight, vital signs, and oxygen saturation by pulse oximetry at rest and after exertion.

2.2.1.2 Confirmation of the diagnosis of RRP by pathology report from a CLIA-certified laboratory (no time limit).

2.2.1.3 Clinic-based flexible nasopharyngolaryngoscopy and/or tracheoscopy to document disease to the extent that can be evaluated without sedation or general anesthesia. This will include standard bright light endoscopy and may include videostroboscopy. Endoscopy may be omitted in patients with disease that is not endoscopically accessible. This examination will allow determination of a Derkay score that will determine if the patient meets inclusion criteria.

2.2.1.4 Computed tomography scan of the neck and/or chest if patients have known or suspected pulmonary RRP. This examination could also be used to determine if the patient meets inclusion criteria.

2.2.1.5 Hepatitis and HIV testing as detailed in sections **2.1.1.9** - **2.1.1.11** (within 90 days prior to subject enrollment).

2.2.1.6 PT/INR and PTT

2.2.1.7 Venous Assessment (per department of transfusion medicine (DTM) guidelines)

2.2.2 Within 3 days prior to subject receiving the first dose of study drug the following assessments will be done:

- CBC w/differential, chemistry panel including: LDH, AST, ALT, ALP, T.Bili, BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, glucose, amylase, lipase, TSH, free T4, free T3
- Pregnancy test in women of childbearing potential.
- Review of medications

2.3 BASELINE EVALUATION

After consenting to enrollment in this study, baseline evaluation will include exam under anesthesia (sedation or general anesthesia) including rigid and/or flexible endoscopy to thoroughly assess airway patency and the extent of disease, rule out invasive cancer, debulk lesions that pose a major risk of airway obstruction, and obtain papilloma and normal mucosa tissue for research. Baseline imaging studies will be done if clinically indicated. For other baseline evaluations please refer to the Study Calendar (Section **3.5**).

2.4 PARTICIPANT REGISTRATION AND STATUS UPDATE PROCEDURES

Registration and status updates (e.g., when a participant is taken off protocol therapy and when a participant is taken off-study) will take place per CCR SOP ADCR-2, CCR Participant Registration & Status Updates found here.

2.4.1 Treatment Assignment and Randomization/Stratification Procedures for Registration Purposes Only

Cohorts

Number	Name	Description
1	*Cohort 1*	*Patients with RRP who are checkpoint inhibitor naïve.*

2	*Cohort 2 (closed to accrual)*	*Patients with RRP who are refractory to checkpoint inhibition.*

Arms

Number	Name	Description
1	*Arm 1*	*Patients will receive 1200 mg IV of M7824 on day 1 of a 14 day cycle, every other week, for up to 12 weeks total treatment (6 cycles).*

Stratification

Not applicable to this protocol.

Randomization

Patients in Cohorts 1 and 2 will be directly assigned to Arm 1. With amendment D, cohort 2 will be closed to further enrollment.

3 STUDY IMPLEMENTATION

3.1 STUDY DESIGN

3.1.1 General study plan

This protocol is a phase II study of M7824. The protocol will enroll subjects with an RRP disease burden that requires repeated surgical procedures for management. Patients with a pathologically confirmed diagnosis of RRP will be screened for this protocol. Patients who appear to be eligible for treatment will be examined via flexible nasopharyngolaryngoscopy and/or tracheoscopy by the Otolaryngology Service. Patients that meet the eligibility criteria will be enrolled onto the study. This study will have two cohorts: (1) patients who are checkpoint inhibitor naive, and (2) patients whose RRP disease is refractory to checkpoint inhibition. After enrollment, patients will undergo exam under anesthesia (EUA) staging of RRP with biopsies to confirm baseline staging, debulk disease that poses an impending airway risk and rule out invasive cancer. Patients will complete the Voice Handicap Index-10 at this time. The voice handicap index-10 (VHI-10) is a patient-based self-assessment tool that quantifies a patients' perception of their voice handicap. It consists of 10 questions that cover three domains: functional, physical and emotional aspects of voice disorders. There is a positive correlation between improvement in anatomic Derkay score and mean VHI-10 score (35).

With amendment D, cohort 2 will be closed to enrollment. Two patients were enrolled and treated on this cohort with no response. Due to the lack of perceived clinical benefit seen thus far in this patient cohort and in previous clinical trials testing M7824 in patients with metastatic HPV-associated cancers that were refractory to checkpoint inhibitors, the checkpoint refractory cohort will be closed to further enrollment.

An optional leukapheresis will be performed prior to the first dose of M7824 (see Section **5.1.1**). If patients are willing, they will also be enrolled on protocol 16C0061 for banking of biospecimens. During EUA, samples for research will be obtained from those patients who enroll on protocol 16C0061 for banking of biospecimens.

M7824 will be administered at a dose of 1200 mg flat dose IV every 2 weeks (+/- 3 days). EUA and endoscopy will be performed to assess airway, RRP lesion inflammation and to obtain research biopsies 2 weeks after the first dose of M7824 (9-17 days after the first dose). An optional leukapheresis will also be obtained at this time point. These procedures should occur before the second dose of M7824. Disease response will first be assessed six weeks after the first dose of M7824 (+/- 10 days), which corresponds to the end of the first course (3 doses) of M7824, by clinic-based endoscopic examination, Voice Handicap Index-10 and imaging if appropriate. These procedures should occur before the Course 2 Cycle 1 Day 1 dose of M7824, if applicable. If patients have a complete response or no response or Disease progression, treatment will be discontinued at that time. If patients have a partial response, treatment will be continued for up to 6 additional weeks (12 weeks total treatment) or until disease progression or complete response. If subjects demonstrate a partial response and receive an additional 6 weeks of treatment their responses will again be measured after completing this additional treatment (+/- 10 days). Patients that have a partial response at the end of course 2 can choose to receive more courses of therapy (maximum of 2) or conclude therapy. Patients will be assessed after each course. At the conclusion of treatment all patients will undergo EUA and endoscopy with either standard of care surgical debulking of their disease or biopsies to confirm complete regression of papillomatous disease. The primary endpoint of this study is complete response to treatment, but patients will be followed long-term after completion of treatment to assess timing and frequency of future interventions.

If a patient's condition precludes safe performance of any protocol-driven biopsy, apheresis or other research procedure, the procedure may be delayed for an additional two weeks or canceled at the discretion of the investigator. This will not be considered a protocol deviation. Endoscopy may be omitted in patients with disease that is not endoscopically accessible.

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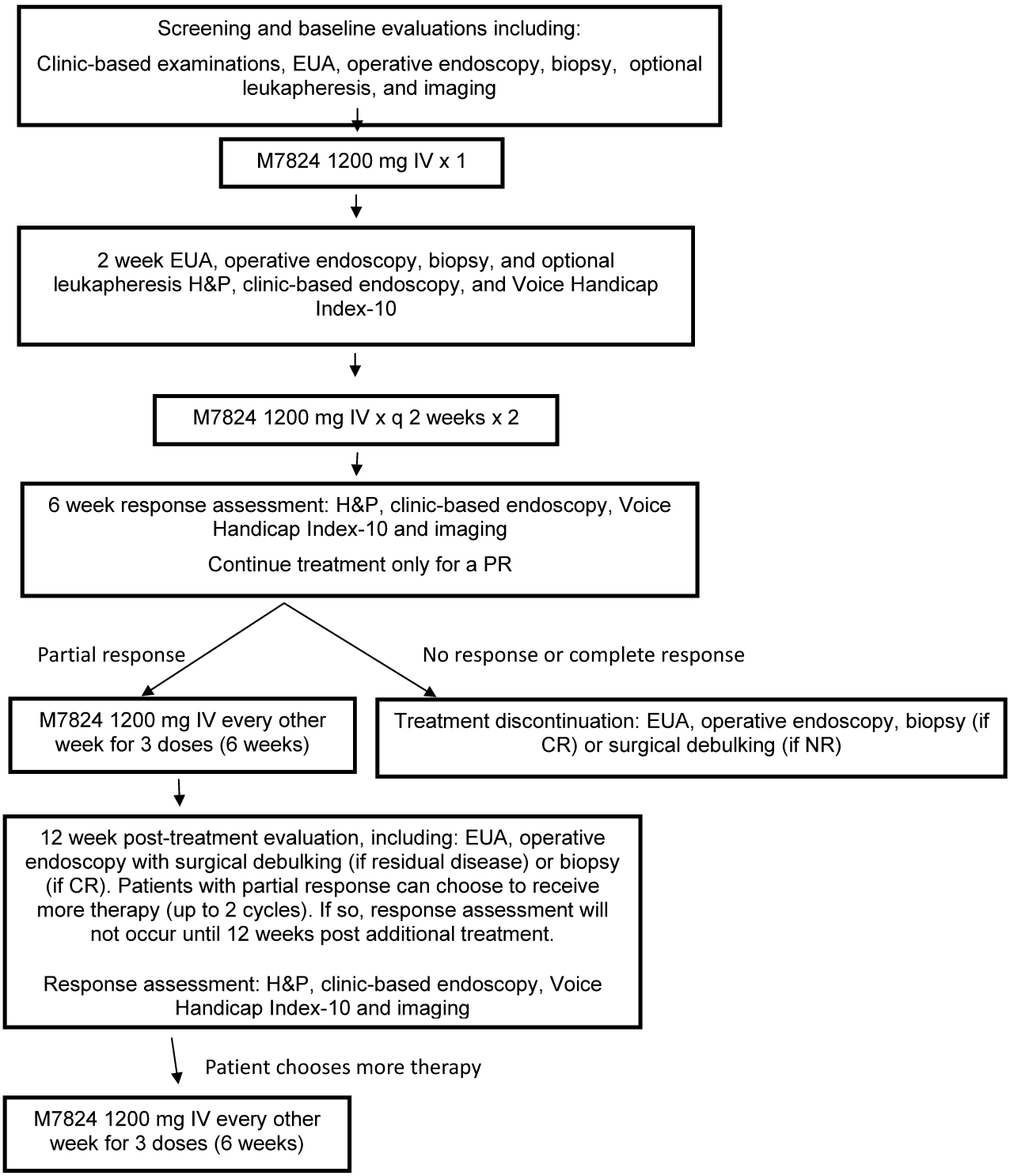
3.1.2 Protocol Schema



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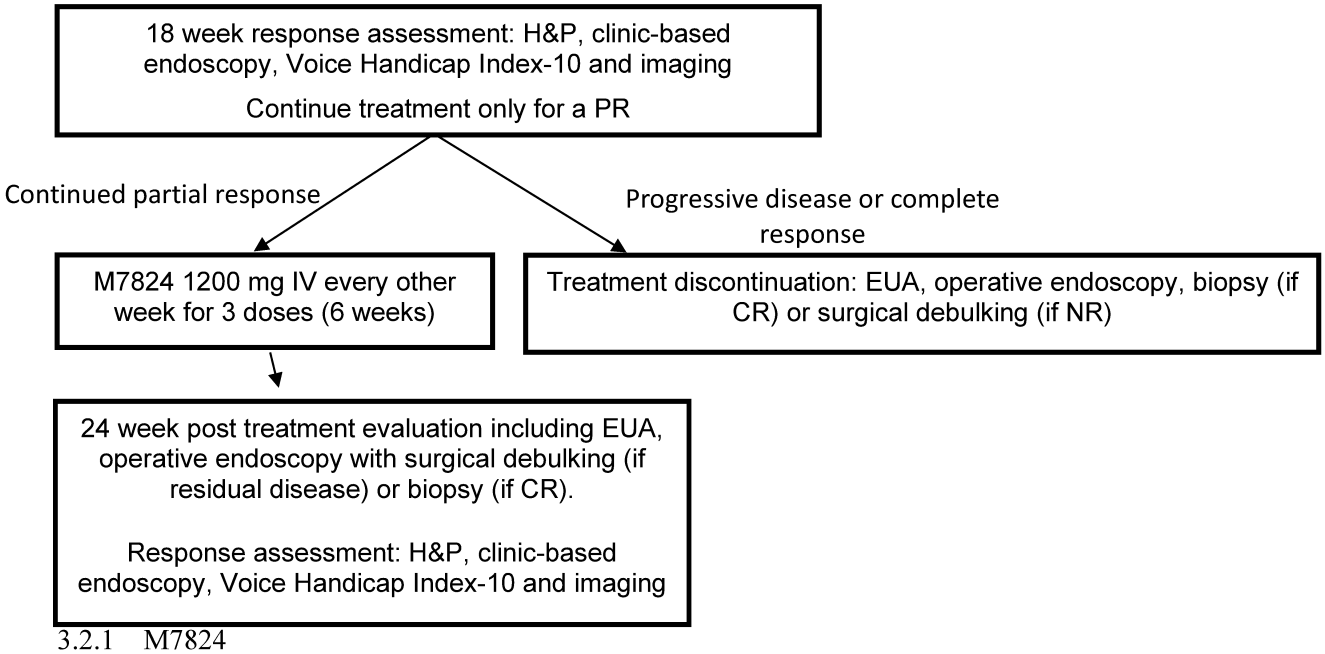

3.2.1 M7824

M7824 will be administered via peripheral IV at a dose of 1200 mg IV every other week for up to 12 weeks total (6 cycles). All patients will be pre-treated with an antihistamine and acetaminophen approximately 30-60 minutes prior to each dose (for example, 25-50 mg diphenhydramine and 500-650 mg acetaminophen). M7824 is to be diluted as described in section **11.1.4**. It is not to be administered as an IV push or bolus injection.

M7824 will be infused at 60 mL/hour for 10 minutes; if no infusion reaction observed then rate will be increased to 120 mL/hour for 10 minutes; if no infusion reaction observed then rate will be increased to 250 mL/hour for the remainder of the infusion. If infusion reactions are observed, the infusion rate may be decreased to the previous rate at which it was tolerated. At the end of the infusion, flush the line with a sufficient quantity of normal saline. See Section **3.4.4** for infusion reaction guidance.

M7824 will be infused in the NIH Clinical Center Day Hospital or on an inpatient oncology ward. Vital signs (blood pressure, pulse, respiration, temperature) will be assessed before infusion, at each rate change, at completion of infusion, and every 1 hour (+/- 15 minutes) or more frequently as clinically indicated for 2 hours after completion of the infusion or until stable.

Medications readily available for the emergency management of anaphylactoid reactions should include: epinephrine (1:1000, 1 mg/mL) for subcutaneous injection, diphenhydramine hydrochloride for intravenous injection, and resuscitation equipment.

3.2.1.1 Overall summary of the treatment plan

Drug	Dose	Days
M7824	1200 mg IV	Day 1 of a 14 day cycle (every other week) for up to 12 weeks total treatment (6 cycles)

Response will be assessed by flexible endoscopy with or without imaging studies before treatment and 6 and 12 weeks after starting treatment. Patients with a partial response at 12 weeks can choose to receive more therapy (maximum of 2 courses). See protocol schema for details on response assessments (section **3.1.2**)

3.3 ON-STUDY ASSESSMENTS

See the section **3.5**, Study calendar for details.

3.4 DOSE MODIFICATIONS/DELAY

Dose modifications are not permitted.

3.4.1 Doses will be delayed for the following:

- Any Grade 2 or greater drug-related adverse event with the following exceptions:
  - Grade 2 skin rash or fatigue
  - Grade 2 infusion reaction in which the full dose of the drug is safely infused, per instructions in section **3.4.4**
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication
- Algorithms for management of toxicities are provided in Section **13.3**

3.4.2 Resuming treatment

Subjects may resume treatment with M7824 under any of the following circumstances:

- Any grade 2 event that resolves to grade 1 or less within 14 days without systemic steroid treatment
- Grade 3/4 rash that improves to Grade 1/2 with treatment
- Grade 2/3/4 endocrinopathy that responds to treatment/replacement therapy

3.4.3 Discontinuing treatment

Treatment should be permanently discontinued for the following:

- Any Grade 3 or 4 drug-related adverse event with the exception of criteria listed in **3.4.2**

3.4.4 M7824 infusion reactions

Since M7824 contains only human immunoglobulin protein sequences it is unlikely to be immunogenic and induce an infusion or hypersensitivity reaction. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypo- or hypertension, bronchospasm, or other symptoms. Infusion reactions should be graded according to NCI CTCAE (version 5.0) guidelines.

NCI-CTCAE Grade	Treatment Modification for Study Drug
Grade 1 – mild Mild transient reaction; infusion interruption not indicated; intervention not indicated.	Remain at bedside and monitor subject until recovery from symptoms. Decrease the study drug infusion rate by 50% and monitor closely for any worsening. Complete the remainder of the infusion at the reduced rate (50% of initial infusion rate). The total infusion time for study drug should not exceed 4 hours.
Grade 2 – moderate Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (for example, antihistamines, NSAIDs, narcotics, corticosteroids, bronchodilators, IV fluids); prophylactic medications indicated for ≤ 24 hours.	Stop study drug infusion. Once infusion-related reaction has resolved or decreased to Grade 1 in severity, resume infusion at 25% of previous rate for 15 minutes, then increase to 50% of previous rate, and monitor closely for any worsening. The total infusion time for study drug should not exceed 4 hours.
Grade 3 or Grade 4 – severe or life-threatening; urgent intervention indicated. Grade 3: Prolonged (for example, 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 ventilator support indicated).	Immediately discontinue infusion of study drug. Begin an IV infusion of normal saline, and treat the subject as follows. Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1,000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Subject should be monitored until the investigator is comfortable that the symptoms will not recur. Study drug will be permanently discontinued. In the case of late-occurring hypersensitivity symptoms (e.g., appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (e.g., oral antihistamine, or corticosteroids). Subjects must be withdrawn immediately from study drug treatment and must not receive any further study drug treatment.

IV = intravenous; NCI-CTCAE = National Cancer Institute-Common Terminology Criteria for Adverse Event; NSAIDs = nonsteroidal anti-inflammatory drugs.

Once the M7824 infusion rate has been decreased by 50% or interrupted due to an infusion-related reaction, it must remain decreased for all subsequent infusions. If a subject experiences a Grade 3 or 4 infusion-related reaction at any time, the subject must discontinue study drug.

3.4.5 Keratoacanthomas

Keratoacanthomas are expected to form in a subset of patients on this protocol. They will not be considered stopping criteria. Patients will be asked at every NIH visit whether they have developed any skin lesions. If they have, the patient will be referred to Dermatology for

characterization and clinical recommendations. The need for intervention should be assessed on a case-by-case basis with input from the primary team, the patient, and the Dermatology consult service.

3.4.6 Severe Hypersensitivity Reactions and Flu-Like Symptoms

If hypersensitivity reaction occurs, the subject must be treated according to the best available medical practice. Subjects should be instructed to report any delayed reactions to the Investigator immediately.

For prophylaxis of flu-like symptoms, 25 mg of indomethacin or comparable nonsteroidal anti-inflammatory drug (NSAID) dose (for example, ibuprofen 600 mg, naproxen sodium 500 mg) may be administered 2 hours before and 8 hours after the start of each dose of M7824 IV infusion. Alternative treatments for fever (for example, paracetamol) may be given to subjects at the discretion of the Investigator.

3.4.7 Tumor Lysis Syndrome

In addition, since M7824 can induce antibody-dependent cell-mediated cytotoxicity, there is a potential risk of tumor lysis syndrome. Should this occur, subjects should be treated per the local guidelines.

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3.5 STUDY CALENDAR

Procedures	Screening	Baseline	Course 1				Course 2 (if indicated)				Courses 3-4 (if indicated)				End of Treatment [a]	Follow-up [q,r]
			Cycle 1 Day 1	Cycle 2 Day 1	Cycle 3 Day 1	End of Course [m]	Cycle 1 Day 1[o]	Cycle 2 Day 1[o]	Cycle 3 Day 1[o]	End of Course [m]	Cycle 1 Day 1[o]	Cycle 2 Day 1[o]	Cycle 3 Day 1[o]	End of Course [m]		
History and PE[b]	X[f]	X[c,e]	X[c,e]	X[c]	X[c]	X	X	X	X	X	X[,]	X	X	X	X	X
Weight	X[f]	X[c,e]	X[c,e]	X[c]	X[c]		X	X	X	X	X[·]	X	X			
Vital signs, O_2 Saturation at rest and after exertion	X	X	X[t]	X[t]	X[t]	X	X[t]	X[t]	X[t]	X	X[t]	X[t]	X[t]	X	X	X
Height		X														
ECOG Performance Score	X[f]															
Confirmation of diagnosis	X															
NIH Advance Directives Form[s]		X														
CBC with differential	X[c,e]	X[c,e]	X[c,e]	X[c]	X[c]	X	X	X	X	X	X[·]	X	X	X	X	X
PT/INR and PTT	X[f]															
Chemistry panel including: LDH, AST, ALT, ALP, T.Bili, BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, glucose, amylase, lipase, TSH, free T4, free T3	X[c,e]	X[c,e]	X[c,e]	X[c]	X[c]	X	X	X	X	X	X	X	X	X	X	X

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Procedures	Screening	Baseline	Course 1				Course 2 (if indicated)				Courses 3-4 (if indicated)				End of Treatment [a]	Follow-up [q,r]
			Cycle 1 Day 1	Cycle 2 Day 1	Cycle 3 Day 1	End of Course [m]	Cycle 1 Day 1[o]	Cycle 2 Day 1[o]	Cycle 3 Day 1[o]	End of Course [m]	Cycle 1 Day 1[o]	Cycle 2 Day 1[o]	Cycle 3 Day 1[o]	End of Course [m]		
Antibody screen for Hepatitis B and C; HIV,	X[p]															
Venous assessment	X															
Pregnancy test	X[c,e]	X[c,e]	X[c,e]	X[c]	X[c]	X	X	X	X	X	X,	X	X	X	X	
TBNK		X,[h]	X[h]	X[c]	X[c]	X	X	X	X	X	X	X	X	X	X	X
HLA Haplotype		X														
Imaging	X[u,f]	X[f]				X[n]				X[n]				X[n]		
ECG		X														
Clinic-based Flexible nasopharyngolaryngoscopy and/or tracheoscopy with Derkay score	X[f]		X[c,e]	X[i]	X[j]	X[k]	X	X[i]	X[j]	X,[k]	X	X[i]	X[j]	X[k]	X	X
Voice Handicap Index-10			X[c]	X[i]	X[j]	X[k]	X	X[i]	X[j]	X[k]	X	X[i]	X[j]	X[k]	X	X
Exam under anesthesia with possible debulking and biopsies [x]			X[h]	X[i]		X[l]				X[l]				X[l]		
Research Blood[v]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events[w]			X	X	X	X	X	X	X	X	X	X	X	X	X	X[d]
Concomitant Medications		X	X[c]	X[c]	X[c]	X	X	X	X	X	X	X	X	X	X	
Optional Leukapheresis			X[h]	X[i]												

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Procedures	Screening	Baseline	Course 1				Course 2 (if indicated)				Courses 3-4 (if indicated)				End of Treatment [a]	Follow-up [q,r]
			Cycle 1 Day 1	Cycle 2 Day 1	Cycle 3 Day 1	End of Course [m]	Cycle 1 Day 1[o]	Cycle 2 Day 1[o]	Cycle 3 Day 1[o]	End of Course [m]	Cycle 1 Day 1[o]	Cycle 2 Day 1[o]	Cycle 3 Day 1[o]	End of Course [m]		
M7824			X	X	X		X	X	X		X	X	X			

[a] End of Treatment studies will be performed 42 days (+/- 10 days) after the final M7824 treatment.

[b] Complete H&P at baseline, directed H&P if clinically indicated before each dose (may include clinic-based flexible nasopharyngolaryngoscopy and/or tracheoscopy), directed H&P at response assessment.

[c] These tests/procedures/assessments must be performed within 3 days before each dose of M7824 while on treatment.

[d] Adverse events will be followed until return to baseline or stabilization of event.

[e] If the screening and baseline tests were performed prior to 3 days before the first dose of M7824, they will need to be repeated before the start of treatment. Refer to section **2.2** for screening evaluation timing requirements.

[f] Within 14 days prior to subject enrollment

[g] Within 28 days prior to subject enrollment

[h] Within 7 days prior to first dose of M7824

[i] 9-17 days after first dose of M7824 (before second dose of M7824)

[j] 9-17 days after second dose of M7824 (before third dose of M7824)

[k] 9-17 days after third dose of M7824 (before the first dose of the next cycle, if applicable)

[l] 9-17 days after last dose of M7824 (if patient does not respond to therapy or has completed all protocol permitted therapy)

[m] +/- 10 days

[n] If imaging is used for response assessment

[o] Tests/procedures/assessments performed for End of Course 1 time point that were completed within 7 days prior to Course 2 Cycle 1 Day1 dose of M7824 do not need to be repeated. Tests/procedures/assessments will be performed within 7 days prior to the next cycle for all subsequent doses. This also applies to Courses 3 and 4 if patient receives these courses.

[p] within 90 days prior to subject enrollment

[q] Patients who experience a complete response or partial response will be evaluated every 6 weeks (following the last dose of study drug) x 3, then every 12 weeks x 3, then every 26 weeks x 2 (+/- 10 days for each time point during the first two years) or until disease progression. After completing the first 2 years' worth of follow up clinic visits, patients will be contacted annually (+/- one month) for 3 years (a total of 5 years follow up) via phone or email for patient status, dates of disease recurrence and interventions to treat recurrent disease. The first follow-up visit (end of treatment), which occurs 42 days (+/- 10 days) after last study treatment, will satisfy safety visit requirements as noted in section **3.6**. If unwilling or unable to travel to the NIH Clinical Center for follow-up visits, patients will be contacted by telephone regarding their status, and may be asked to send labs and physical exam reports to fulfill visit requirements.

[r] Patients who do not experience a response to treatment will be contacted annually (+/- one month) for 2 years following the last dose of study drug to document additional disease recurrence and treatments that they have received. For the safety follow-up visit which should occur approximately 42 days (+/- 10 days) after last study treatment (as noted in section **3.6**), if unwilling or unable to travel to the NIH Clinical Center, patients will be contacted by telephone regarding their status, and may be asked to send labs and physical exam reports to fulfill end of treatment safety follow-up visit requirements. Annual follow-up contact may occur via telephone or email.

[s] As indicated in section **10.4,** all subjects will be offered the opportunity to complete an NIH advance directives form. This should be done preferably at baseline but can be done at any time during the study as long as the capacity to do so is retained. The completion of the form is strongly recommended, but is not required.

[t] As noted in Section **3.2.1**.

[u] Computed tomography scan of the neck and/or chest only if patients have known or suspected pulmonary RRP. See Section **2.2.1.4**.

[v] See section **5.1** for information on specimen collection timepoints.

[w] Adverse events will be assessed prior to each dose of M7824 and every week by telephone between on-site assessments (Telephone communication with patient to assess for any symptoms suggestive of an adverse event; this will be performed by physician or research nurse. Symptoms of myocarditis (chest pain, shortness of breath, swelling of ankles or feet, bleeding) will be assessed).

[x] EUA with possible debulking may be performed at any time if clinically indicated.

3.6 COST AND COMPENSATION

3.6.1 Costs

NIH does not bill health insurance companies or participants for any research or related clinical care that participants receive at the NIH Clinical Center. If some tests and procedures performed outside the NIH Clinical Center, participants may have to pay for these costs if they are not covered by insurance company. Medicines that are not part of the study treatment will not be provided or paid for by the NIH Clinical Center.

3.6.2 Compensation

Participants will not be compensated on this study.

3.6.3 Reimbursement

The NCI will cover the costs of some expenses associated with protocol participation. Some of these costs may be paid directly by the NIH and some may be reimbursed to the participant/guardian as appropriate. The amount and form of these payments are determined by the NCI Travel and Lodging Reimbursement Policy.

3.7 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

Prior to documenting removal from study, effort must be made to have all subjects complete a safety visit approximately 42 days (+/- 10 days) following the last dose of study therapy.

3.7.1 Criteria for removal from protocol therapy

Patients will be taken off treatment for the following:

- Requirement for therapy prohibited by protocol (see section **4.2**)
- Completion of protocol therapy
- Participant requests to be withdrawn from active therapy
- The patient receives any other treatment for RRP or requires the use of any corticosteroids (> 10 mg daily prednisone equivalents) or other immunosuppressive medications
- General or specific changes in the patient's condition render the patient unacceptable for further treatment on this study in the judgment of the investigator
- Any Grade 3/4 drug-related adverse events with the exceptions as detailed in section **3.4**
- Disease progression
- Participant becomes pregnant
- Investigator discretion

3.7.2 Duration of Follow up

Patients who do not experience a response (See section **6.3.3.1**) will be contacted via phone or email annually for two years after the 42 day (+/- 10 days) follow up visit to determine the date of disease recurrence following completion debulking on this study and the dates and types of additional interventional procedures to control RRP. Patients who experience a complete response or partial response will be evaluated every 6 weeks (following the last dose of study drug) x 3, then every 12 weeks x 3, then every 26 weeks x 2 (+/- 10 days for each time point during the first two

years) or until disease progression. After completing the first 2 years' worth of follow up clinic visits, patients will be contacted annually (+/- one month) for 3 years (a total of 5 years follow up) via phone or email for patient status, dates of disease recurrence and interventions to treat recurrent disease. The dates of disease recurrence and interventions to treat recurrent disease will be recorded.

3.7.3 Off-Study Criteria

Patients will be taken off study for the following:

- The patient voluntarily withdraws
- There is significant patient noncompliance
- The investigators decide to end the study
- The investigators decide it is in the patient's best interest
- The patient completes off treatment follow-up
- Death

3.8 STOPPING RULE

3.8.1 The study will be halted (immediately stop accrual and treatment) if any of the following safety conditions are met and we will promptly investigate and submit an amendment to the IRB and FDA if necessary:

- Any treatment-related death
- Three ≥ Grade 3 Unexpected Serious Adverse Events that are at least possibly related to the study drug
- Any bleeding/hemorrhage leading to a serious adverse event

3.8.2 All protocol treatment will be temporarily stopped to allow review of interim summary of safety and efficacy following completion of the pilot cohort prior to expanding enrollment.

4 CONCOMITANT MEDICATIONS/MEASURES

4.1 SUPPORTIVE CARE

Epinephrine (1:1000, 1 mg/m subcutaneous injection), diphenhydramine hydrochloride (intravenous injection), and resuscitation equipment may be used during the study in the emergency management of anaphylactoid reactions.

Further supportive per NIH CC Pharmacy guidelines is permitted with the exception of interventions appearing in section **4.2**.

4.2 PROHIBITED THERAPIES

- Vaccination during treatment is prohibited.
- Any corticosteroids (> 10 mg daily prednisone equivalents) or other immunosuppressive medications.

5 BIOSPECIMEN COLLECTION

Biospecimen collection on this protocol will consist of blood draws, leukapheresis products, and biopsies of papillomas and adjacent tissue.

Sample	Collection Details*	Timepoints	Location of specimen analysis
Blood Samples			
Whole Blood	96 mL (12 x 8 mL CPT tubes) 48 mL (6 x 8 mL CPT tubes)	Prior to first dose of M7824 Prior to each M7824 dose, End of Treatment, Followup	Pre-Clinical Core lab (Jeremy Rose)
Serum	16 mL (2 x 8 mL SST tubes) 8mL (1 x 8 mL SST tube)	Within 14 days prior to first dose of M7824 Prior to each M7824 dose, End of Treatment, Followup	Pre-Clinical Core lab (Jeremy Rose)
Apheresis Sample (optional)	100 mL or less	Prior to first and second dose of M7824 during Course 1	Pre-Clinical Core lab (Jeremy Rose)
Tissue Samples			
Papilloma Biopsy	Up to 10 papilloma fragments, each 1-3 mm in diameter. Up to two fragments of normal mucosa, each 1-3 mm in diameter.	Prior to treatment during course 1 on C1D1, C2D1 (9-17 days after first dose of M7824 and before second dose of M7824); end of Course if non-responder or completion of protocol allowed therapy, and if debulking is performed	NCI Laboratory of Pathology (for review and archiving) Processed in Christian Hinrichs Lab, then transported to Pre-Clinical Core lab (Jeremy Rose)
*Tubes/media may be adjusted at the time of collection based upon materials available. The amount of blood that may be drawn from adult patients for research purposes shall not exceed 10.5 mL/kg or 550 mL, whichever is smaller, over any eight-week period.			

Sample	Collection Details*	Timepoints	Location of specimen analysis
NOTE: Portions of all samples may be banked for future research analyses; prospective consent will be obtained during the informed consent process.			

5.1 CORRELATIVE STUDIES FOR RESEARCH

5.1.1 Biospecimen collection before the start of M7824

- Patients will also be invited to enroll on protocol 16C0061 for which patients must consent separately.
- Blood will be collected for research purposes. A total of 12 CPT tubes (8 mL each of blood) may be collected prior to the first dose of M7824. This is a total of 96 mL of blood. This blood may be used for immunology assays. This blood can be collected on different days as long as a total of 12 CPT tubes are collected prior to the first dose of M7824. One CPT tube may be used to collect plasma which may be frozen in a 4mL vial. PBML from the remainder of the CPT tubes may be frozen in aliquots of 10×10^6 cells/vial. Send to the Pre-Clinical Core lab; Attention Jeremy Rose, Bldg. 10, room 12C216 contact phone: 301-594-5339.
- 16 mL of blood may be drawn to obtain serum for research purposes (2 SST tubes, 8 mL per tube) within 14 days prior to the first dose of M7824. This will be processed in ETIB Pre-Clinical Core and frozen in aliquots of 0.5-1mL/vial. Send to the Pre-Clinical Core lab; Attention Jeremy Rose, Bldg. 10, room 12C216 contact phone: 301-594-5339.
- TBNK (within 7 days prior to the first dose of M7824)
- HLA typing will be performed at baseline to facilitate immunotherapy assays.
- The patient has the option to undergo an approximately 5-liter research apheresis (target yield 100 mL). This will be performed prior to first dose of M7824. Apheresis will only be performed on patients with adequate peripheral venous access. Cells will be transferred to the Pre-Clinical Core lab, Attention Jeremy Rose, Bldg. 10, room 12C216, contact phone: 301-594-5339. Aliquots of PBMC and plasma will be cryopreserved for immunological monitoring. Cell product will be frozen in 10 vials at concentration 100 x106 cells/mL and additional vials at 300 x 106 cells/mL.
- Papilloma and adjacent tissue samples will be collected by biopsy prior to the first dose of M7824. Biopsies will be obtained with rigid or flexible endoscopy under sedation or general anesthesia. They will consist of up to 10 papilloma fragments, each 1-3 mm in diameter. One fragment may be sent to pathology for permanent sections. The other fragments of the biopsy will be sent to Dr. Hinrichs' laboratory in sterile 1.5 mL Eppendorf tubes with a small amount of sterile normal saline. Additional tissue that is removed to debulk papillomas may also be collected for research. Up to two fragments of normal mucosa, each 1-3 mm in diameter, will also

be obtained and sent to Dr. Hinrichs' laboratory. Send to Dr. Hinrichs' lab; Building 10, Room 4B04; Attention: Megan Kenyon, CRNP 240-858-3667.

- Patients with papillomas that cannot be biopsied by endoscopy may participate in the trial. All tissue specimen collection except papilloma biopsies will be performed.
- Specimens will be cataloged and stored in the Pre-Clinical Core lab. Assays will be performed retrospectively.

5.1.2 Biospecimen collection during treatment and follow-up

- Patients will return to the Clinical Center every two weeks for M7824 dosing. Blood and serum for research and TBNK testing may be obtained prior to each dose of M7824, at the End of Treatment visit and at follow-up visits. Blood for research may consist of:
  - 6 CPT tubes of Research Blood (48 mL) may be collected for immunological testing and processed as described in section **5.1.1**. Attention Jeremy Rose, Bldg. 10, room 12C216 contact phone: 301-594- 5339.
  - 1 SST tube (8 mL) of Research Blood may be obtained for serum collection and processed as described in section **5.1.1** . Attention Jeremy Rose, Bldg. 10, room 12C216 contact phone: 301-594-5339.
- Papilloma and adjacent tissue samples will be collected by biopsy 9-17 after the first dose of M7824. This should occur prior to second dose of M7824. Biopsies will again be collected at the time of completion debulking.. Biopsies will be obtained with rigid or flexible endoscopy under sedation or general anesthesia. They will consist of up to 10 papilloma fragments, each 1-3 mm in diameter. One fragment may be sent to pathology for permanent sections. The other fragments of the biopsy will be sent to Dr. Hinrichs' laboratory in sterile 1.5 mL Eppendorf tubes with a small amount of sterile normal saline. Up to two fragments of normal mucosa, each 1-3 mm in diameter, will also be obtained and sent to Dr. Hinrichs' laboratory. Send to Dr. Hinrichs' lab; Building 10, Room 4B04; Attention: Megan Kenyon, CRNP 240-858-3667.
- The patient has the option to undergo an approximately 5-liter research apheresis (target yield 100 mL). This apheresis should occur before the second dose of M7824 during Course 1 only. Apheresis will only be performed on patients with adequate peripheral venous access. Cells will be transferred to the Pre-Clinical Core lab, Attention Jeremy Rose, Bldg. 10, room 12C216, contact phone: 301-594-5339. Aliquots of PBMC and plasma may be cryopreserved for immunological monitoring. Cell product may be frozen in 10 vials at concentration 100 x106 cells/mL and additional vials at 300 x 106 cells/mL.
- If patients experience a partial or complete response, they will continue to be followed every 6 weeks x 3, then every 12 weeks x 3, then every 26 weeks x 2. Research blood and TBNK may be collected at these time points as described above.

5.1.3 Research studies

- Biospecimens will be collected for research to identify biomarkers of response, understand the mechanism of action of the treatment, and investigate the biology of RRP.

- Research studies will be considered exploratory analyses and may include: assessment of PD-L1 expression by papillomas and papilloma-infiltrating immune cells, testing of papillomas and normal appearing mucosa for HPV, evaluation of papillomas by nanostring and evaluation of papilloma-infiltrating T cell responses against HPV antigens.
  - Testing of papilloma-infiltrating T cells and peripheral blood T cells for recognition of HPV antigens (30).

    Generation and isolation of T cells

    Papilloma-infiltrating T cells may be generated from papilloma biopsy specimens by culture of 2 mm tissue fragments in culture media with IL-2. Lymphocyte cultures may be split when confluent and cryopreserved when sufficient cells have been generated. Flow cytometry may be performed to assess the lymphocyte populations using markers such as CD3, CD4, CD8, and CD56 to assess lymphocyte subtypes. T cells may be isolated from peripheral blood samples by magnetic bead separation using standard techniques from commercially available kits (Miltenyi or similar).

    HPV-specific T cell response assays

    Target cells for assays measuring HPV-specific T cells responses may be autologous immature dendritic cells (DCs) generated from apheresis samples. The DCs may be loaded with pools of overlapping peptides spanning each of the viral antigens encoded by HPV. Reactivity against each antigen will be assessed separately. Immunological assays may consist of interferon-gamma ELISPOT, interferon-gamma production as determined by ELISA, 4-1BB upregulation, and or intracellular cytokine production as described previously (30).

    HPV detection and genotyping

    Testing will be performed by Dr. Hinrichs' laboratory using PCR-based type-specific HPV detection and quantification assays (30).

5.1.4 Co-Enrollment on 16C0061 / Biobanking

Samples from patients may be transferred to protocol 16C0061 for biobanking of specimens if the patient has consented to that study.

5.1.5 Sample Storage, Tracking and Disposition

5.1.5.1 Storage/Tracking in the Preclinical Development and Clinical Monitoring Facility (PDCMF)

- Samples will be ordered in CRIS and tracked through a Clinical Trial Data Management system. Should a CRIS screen not be available, the CRIS downtime procedures will be followed. Samples will not be sent outside NIH without appropriate approvals and/or agreements, if required.
- Samples will be archived by the ETIB Preclinical Development and Clinical Monitoring Facility (PDCMF). All data associated with archived clinical research samples is entered into LabMatrix. Access to this folder is limited to PDCMF staff and ETIB clinical staff,

requiring individual login and password. All staff in the PDCMF laboratory receives annually updated NIH/CIT training and maintains standards of computer security.

- The data recorded for each sample includes the patient ID, trial name/protocol number, date drawn, treatment cycle/post-transplant time point, cell source (e.g. peripheral blood, lymph apheresis, mobilized peripheral blood stem cells, marrow, urine, skin or oral biopsy) as well as box and freezer location. Patient demographics that correlate treatment outcomes and therapies with the samples can be obtained only through the NCI/ETIB clinical records. As of January 2007, all newly received samples receive a unique bar code number, which is included in the sample record in the PDCMF database. Only this bar code is recorded on the sample vial and the vials will not be traceable back to patients without authorized access to the PDCMF database. All non-coded samples previously archived will be stripped of identifiers prior to distribution for any use other than as a primary objective of the protocol under which they were collected.
- Samples are stored in locked freezers. All samples will be labeled solely with a bar code (which includes the date, and serially determined individual sample identifier). The key will be available to a restricted number of ETIB investigators and associate investigators on the protocol. Coded samples will be stored frozen at -20°, -80° or liquid nitrogen vapor phase according to the stability requirements under the restricted control of the PDCM Facility of ETIB.
- Access to samples from a protocol for research purposes will be by permission of the Principal Investigator of that protocol in order to be used (1) for research purposes associated with protocol objectives for which the samples were collected, or (2) for a new research activity following submission and IRB approval of a new protocol and consent, or (3) for use only as unlinked or coded samples under the OHSRP Exemption Form guidelines stipulating that the activity is exempt from IRB review. Unused samples must be returned to the PDCMF laboratory.
- Samples, and associated data, will be stored permanently unless the patient withdraws consent. If researchers have samples remaining once they have completed all studies associated with the protocol, they must be returned to the PDCMF laboratory.
- These freezers are located onsite at the PDCMF laboratory (12C216) or in ETIB common equipment space (CRC/3-3273).

5.1.5.2 Hinrichs laboratory

- Samples may be transferred from Preclinical Development and Clinical Monitoring Facility to the Hinrichs laboratory for the research studies indicated in **5.1.3**.
- Samples transferred to the Hinrichs laboratory will be barcoded and tracked with LabMatrix.
- Laboratory research data will be stored on the NCI secure server in the Hinrichs laboratory folder with secure access by laboratory personnel only.

5.1.5.3 Protocol Completion/Sample Destruction

- Once research objectives for the protocol are achieved, researchers can request access to remaining samples, providing they have both approval of the Principal Investigator of the original protocol under which the samples or data were collected and either an IRB

approved protocol and patient consent or the OHSRP Exemption Form stipulating that the activity is exempt from IRB review.

- The PDCMF staff will report to the Principal Investigators any destroyed samples, if samples become unsalvageable because of environmental factors (ex. broken freezer or lack of dry ice in a shipping container), lost in transit between facilities or misplaced by a researcher.
- The PI will record any loss or unanticipated destruction of samples as a deviation. Reports will be made per the requirements of section **7.2**.

6 DATA COLLECTION AND EVALUATION

6.1 DATA COLLECTION

The PI will be responsible for overseeing entry of data into the C3D electronic system and ensuring data accuracy, consistency and timeliness. The principal investigator, associate investigators/research nurses and/or a contracted data manager will assist with the data management efforts. All data obtained during the conduct of the protocol will be kept in secure network drives or in approved alternative sites that comply with NIH security standards. Primary and final analyzed data will have identifiers so that research data can be attributed to an individual human subject participant.

End of study procedures: Data will be stored according to HHS, FDA and NIH Intramural Records Retention Schedule as applicable.

Loss or destruction of data: Should we become aware that a major breach in our plan to protect subject confidentiality and trial data has occurred this will be reported expeditiously per requirements in section **7.2.1**.

6.1.1 Adverse event recording

- Grade 1 adverse events will not be recorded.
- Grade 2 adverse events that will be recorded:
    a. Unexpected events that are possibly, probably, or definitely related to the research.
    b. Expected events that are probably or definitely related to the study interventions will be record only for the first year.
    c. Any serious events that are deemed clinically significant by the PI

  Note: Grade 2 adverse events that are clearly attributable to surgery/procedure will not be recorded.
- Adverse Events that occur during the follow-up period will only be recorded if they are considered related to the M7824.
- All grade 3, 4, and 5 adverse events will be recorded regardless of attribution.
- All adverse events are recorded in the medical record.

All adverse events, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed until return to baseline or stabilization of event.

Document AEs from the first administration of the study therapy, Study Day 1, through 42 days after the study therapy was last administered. Beyond 42 days after the last administration, only adverse events which are serious and related to the study intervention need to be recorded.

An abnormal laboratory value will be considered an AE if the laboratory abnormality is characterized by any of the following:

- Results in discontinuation from the study
- Is associated with clinical signs or symptoms
- Requires treatment or any other therapeutic intervention
- Is associated with death or another serious adverse event, including hospitalization.
- Is judged by the Investigator to be of significant clinical impact
- If any abnormal laboratory result is considered clinically significant, the investigator will provide details about the action taken with respect to the test drug and about the patient's outcome.

6.1.2 Concomitant medications recording

Only medications used to treat adverse events related to the study medication will be recorded in the data base.

6.1.3 Collection of recurrence and subsequent treatments

The dates of disease recurrences following completion of treatment and/or debulking on this study and the dates and types of additional interventional procedures to control RRP will be recorded.

6.2 DATA SHARING PLANS

6.2.1 Human Data Sharing Plan

What data will be shared?

I will share human data generated in this research for future research as follows:

_x__ Coded and linked data in an NIH-funded or approved public repository.

_x__ Coded and linked data in BTRIS (automatic for activities in the Clinical Center)

_x__ Coded and linked or identified data with approved outside collaborators under appropriate agreements.

How and where will the data be shared?

Data will be shared through:

_x__ An NIH-funded or approved public repository. Insert name or names:ClinicalTrials.gov.

_x__ BTRIS (automatic for activities in the Clinical Center)

_x__ Approved outside collaborators under appropriate individual agreements.

_x__ Publication and/or public presentations.

When will the data be shared

_x__ Before publication.

_x__ At the time of publication or shortly thereafter.

6.3 RESPONSE CRITERIA

Disease stage and response will be determined by flexible nasopharyngolaryngoscopy and/or tracheoscopy using the Derkay staging system if the patient does not have pulmonary disease and/or by imaging if the patient has pulmonary disease (6). The Derkay staging system has been validated with a high degree of inter-rater reliability (31). It incorporates an objective score based on the number of sites and bulkiness of papillomas within the pharynx, larynx and trachea and a subjective score determined by voice and breathing symptoms. Physical exam and/or clinic-based endoscopy will be used to visualize all accessible papillomas and assign an objective score using the Derkay system. Only lesions that can be visualized by clinic-based flexible nasopharyngolaryngoscopy and/or tracheoscopy will be included in the baseline score used for assessing treatment response. This score must be 10 or greater for patients to be eligible for treatment. If patients have disease that is better visualized or only visualized with an imaging study such as CT scan or MRI then imaging studies will be obtained. Preliminary Derkay scores and response assessment will be determined by the endoscopist performing the procedure. Final reporting of clinical responses will be based on a blinded review of endoscopic video and or photos by one or more independent otolaryngologists.

Response and progression from imaging studies will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) (32). Changes in the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST criteria.

If a subject has disease being assessed by imaging for response and refuses clinic-based flexible nasopharyngolaryngoscopy and/or tracheoscopy, no Derkay score will be calculated. This will not be considered a protocol deviation.

6.3.1 Baseline assessment

- All accessible disease will be examined by physical exam and/or endoscopy to establish a baseline
- Only lesions visualized by clinic-based flexible nasopharyngolaryngoscopy and/or tracheoscopy will be included in the baseline objective Derkay score
- Imaging studies will be performed if appropriate and baseline measurements determined using RECIST 1.1 criteria

6.3.2 Definition of measurable disease

- Any papilloma that can be visualized via clinic-based endoscopy and assigned a score using the Derkay system
- Any papilloma that can be measured by imaging using RECIST 1.1 criteria

6.3.3 Definition of disease response

6.3.3.1 Complete Response (CR)

All criteria must be met.

- No evidence of papillomas on physical exam and/or clinic-based flexible nasopharyngolaryngoscopy and/or tracheoscopy
- No evidence of papillomas by exam under anesthesia (sedation or general anesthesia) with endoscopy and biopsies
- Absence of disease by imaging if lesions are assessed by imaging

6.3.3.2 Partial response (PR)

Either criterion may be met.

- Decrease in Derkay anatomic score of 30 percent or greater
- Partial tumor response by imaging using RECIST 1.1 criteria

6.3.3.3 Progressive disease (PD)

Any criterion may be met.

- Increase in objective Derkay anatomic score of 50 percent or greater
- Disease progression by imaging using RECIST 1.1 criteria
- New or worsening symptoms attributable to growth of papillomas or new papillomas

6.3.3.4 Stable disease

- Not meeting criteria for CR, PR, or PD

6.3.4 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Patients with Measurable Disease (i.e., Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	

SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.

** Only for non-randomized trials with response as primary endpoint.

*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration."* Every effort should be made to document the objective progression even after discontinuation of treatment.

6.4 TOXICITY CRITERIA

The following adverse event management guidelines are intended to ensure the safety of each patient while on the study. The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm).

7 NIH REPORTING REQUIREMENTS/DATA AND SAFETY MONITORING PLAN

7.1 DEFINITIONS

Please refer to definitions provided in Policy 801: Reporting Research Events found here.

7.2 OHSRP OFFICE OF COMPLIANCE AND TRAINING / IRB REPORTING

7.2.1 Expedited Reporting

Please refer to the reporting requirements in Policy 801: Reporting Research Events and Policy 802 Non-Compliance Human Subjects Research found here. Note: Only IND Safety Reports that meet the definition of an unanticipated problem will need to be reported per these policies.

7.2.2 IRB Requirements for PI Reporting at Continuing Review

Please refer to the reporting requirements in Policy 801: Reporting Research Events found here.

7.3 NCI CLINICAL DIRECTOR REPORTING

Problems expeditiously reported to the OHSRP/IRB in iRIS will also be reported to the NCI Clinical Director. A separate submission is not necessary as reports in iRIS will be available to the Clinical Director.

In addition to those reports, all deaths that occur within 30 days after receiving a research intervention should be reported via email to the Clinical Director unless they are due to progressive disease.

To report these deaths, please send an email describing the circumstances of the death to Dr. Dahut at NCICCRQA@mail.nih.gov within one business day of learning of the death.

7.4 NIH Required Data and Safety Monitoring Plan

7.4.1 Principal Investigator/Research Team

The clinical research team will meet every two weeks when patients are being actively treated on the trial to discuss each patient. Decisions about dose level enrollment and dose escalation if applicable will be made based on the toxicity data from prior patients.

All data will be collected in a timely manner and reviewed by the principal investigator. Events meeting requirements for expedited reporting as described in section **7.2.1** will be submitted within the appropriate timelines.

The principal investigator will review adverse event and response data on each patient to ensure safety and data accuracy. The principal investigator will personally conduct or supervise the investigation and provide appropriate delegation of responsibilities to other members of the research staff.

8 SPONSOR SAFETY REPORTING

8.1 Definitions

8.1.1 Adverse Event

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (ICH E6 (R2))

8.1.2 Serious Adverse Event (SAE)

An adverse event or suspected adverse reaction is considered serious if in the view of the investigator or the sponsor, it results in any of the following:

- Death,
- A life-threatening adverse event (see **8.1.3**)
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect.
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon

appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

8.1.3 Life-threatening

An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death. (21CFR312.32)

8.1.4 Severity

The severity of each Adverse Event will be assessed utilizing the CTCAE version 5.0.

8.1.5 Relationship to Study Product

All AEs will have their relationship to study product assessed using the terms: related or not related.

- Related – There is a reasonable possibility that the study product caused the adverse event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study product and the adverse event.
- Not Related – There is not a reasonable possibility that the administration of the study product caused the event.

8.2 Assessment of Safety Events

AE information collected will include event description, date of onset, assessment of severity and relationship to study product and alternate etiology (if not related to study product), date of resolution of the event, seriousness and outcome. The assessment of severity and relationship to the study product will be done only by those with the training and authority to make a diagnosis and listed on the Form FDA 1572 as the site principal investigator or sub-investigator. AEs occurring during the collection and reporting period will be documented appropriately regardless of relationship. AEs will be followed through resolution.

SAEs will be:

- Assessed for severity and relationship to study product and alternate etiology (if not related to study product) by a licensed study physician listed on the Form FDA 1572 as the site principal investigator or sub-investigator.
- Recorded on the appropriate SAE report form, the medical record and captured in the clinical database.
- Followed through resolution by a licensed study physician listed on the Form FDA 1572 as the site principal investigator or sub-investigator.

For timeframe of recording adverse events, please refer to section **6.1**.

8.3 Reporting of Serious Adverse Events

Any AE that meets protocol-defined serious criteria or meets the definition of Adverse Event of Special Interest that require expedited reporting must be submitted immediately (within 24 hours of awareness) to OSRO Safety using the CCR SAE report form.

All SAE reporting must include the elements described in **8.2**.

SAE reports will be submitted to the Center for Cancer Research (CCR) at: OSROSafety@mail.nih.gov and to the CCR PI and study coordinator. CCR SAE report form and instructions can be found at: https://ccrod.cancer.gov/confluence/pages/viewpage.action?pageId=157942842

Following the assessment of the SAE by OSRO, other supporting documentation of the event may be requested by the OSRO Safety and should be provided as soon as possible.

8.4 Safety Reporting Criteria to the Pharmaceutical Collaborators

8.4.1 To be sent by OSRO Safety:

8.4.1.1 Serious and Unexpected Suspected Adverse Reaction (SUSAR)

Definition: A suspected adverse reaction to study treatment that is both serious and unexpected. The sponsor must report SUSARs within 2 business days of learning of the event to EMD Serono's parent company, Merck via Fax: 781-681-2961 or email: gds@merckgroup.com.

8.4.1.2 Serious Adverse Event (SAE)

Definition: See Section **7.1**. The sponsor must report SAEs within 2 business days of learning of the event to EMD Serono's parent company, Merck via Fax: 781-681-2961 or email: gds@merckgroup.com.

8.4.1.3 Pregnancy

The sponsor must report any pregnancy occurring in a subject treated with the study drug during the course of the study. The Investigator shall ensure that the case is followed up to the end of the pregnancy and provide all relevant documentation and a final report on the outcome to Merck.

8.4.1.4 Annual Report

The sponsor will provide a copy of the FDA Annual Report to EMD Serono/Merck at the time of submission to the FDA.

8.5 Reporting Pregnancy

8.5.1 Maternal exposure

If a patient becomes pregnant during the course of the study, the study treatment should be discontinued immediately, and the pregnancy reported to the Sponsor no later than 24 hours of when the Investigator becomes aware of it. The Investigator should notify the Sponsor no later than 24 hours of when the outcome of the Pregnancy become known,

Pregnancy itself is not regarded as an SAE. However, congenital abnormalities or birth defects and spontaneous miscarriages that meet serious criteria (**8.1.2**) should be reported as SAEs.

The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) should be followed up and documented.

8.5.2 Paternal exposure

Male patients should refrain from fathering a child or donating sperm during the study and for 60 days after the last dose of M7824.

Pregnancy of the patient's partner is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) occurring from the date of the first dose of M7824 until 60 days after the last dose should, if possible, be followed up and documented.

8.6 REGULATORY REPORTING FOR STUDIES CONDUCTED UNDER CCR-SPONSORED IND

Following notification from the investigator, CCR, the IND sponsor, will report any suspected adverse reaction that is both serious and unexpected. CCR will report an AE as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the study product and the adverse event. CCR will notify FDA and all participating investigators (i.e., all investigators to whom the sponsor is providing drug under its INDs or under any investigator's IND) in an IND safety report of potential serious risks from clinical trials or any other source, as soon as possible, in accordance to 21 CFR Part 312.32.

All serious events will be reported to the FDA at least annually in a summary format.

9 CLINICAL MONITORING

As a sponsor for clinical trials, FDA regulations require the CCR to maintain a monitoring program. The CCR's program allows for confirmation of: study data, specifically data that could affect the interpretation of primary and secondary study endpoints; adherence to the protocol, regulations, ICH E6, and SOPs; and human subjects protection. This is done through independent verification of study data with source documentation focusing on:

- Informed consent process
- Eligibility confirmation
- Drug administration and accountability
- Adverse events monitoring
- Response assessment.

The monitoring program also extends to multi-site research when the CCR is the coordinating center.

This trial will be monitored by personnel employed by a CCR contractor. Monitors are qualified by training and experience to monitor the progress of clinical trials. Personnel monitoring this study will not be affiliated in any way with the trial conduct.

10 STATISTICAL CONSIDERATIONS

10.1 STATISTICAL HYPOTHESES

10.1.1 Primary Efficacy Endpoints

The primary efficacy endpoint is the fraction of patients in each cohort who have a complete response.

10.1.2 Secondary Efficacy Endpoints

The secondary efficacy endpoint is the fraction of patients in each cohort who have a partial response.

10.1.3 Sample Size Determination

Patients will be enrolled into one of two cohorts according to whether they are checkpoint inhibitor naïve or have RRP disease which is refractory to checkpoint inhibition. In each of the two cohorts, the trial will be conducted using a Simon minimax two-stage design; the objective is to rule out a 5% complete response rate (p0=0.05) and target a 20% complete response rate (p1=0.20).

With amendment D, cohort 2 will be closed to further enrollment.

The design will use alpha=0.10 (10% chance of accepting a poor agent) and beta=0.20 (corresponding to 80% power--and 20% chance of incorrectly rejecting a promising agent). The first stage of accrual will consist of 12 evaluable patients. If 0/12 has a complete clinical response, then no further patients would be enrolled to that cohort. Should 1 or more patients in the first 12 have a complete response, then accrual would continue until a total of 21 evaluable patients have enrolled in that cohort. If there are 1 to 2 complete responses in 21 evaluable patients in a cohort, this would be considered unacceptably low, while if 3 or more evaluable patients have complete responses in 21 patients in a cohort (14.3%), then the results will be considered sufficiently promising for further evaluation in that cohort. Under the null hypothesis (5% complete response rate), the probability of early termination is 54.0%.

It is anticipated that up to 1 patient per month may enroll onto this trial; thus, 2 to 3 years may be required to complete accrual. The trial would require up to 21 total evaluable patients in cohort 1; the accrual ceiling will be set at 26 patients to allow for a small number of inevaluable patients as well as to accommodate the 2 subjects enrolled in cohort 2 prior to its closure.

10.1.4 Populations for Analysis

Modified intention to treat: all patients who receive at least one dose of the agent will be included in the statistical analyses performed.

10.2 STATISTICAL ANALYSES

10.2.1 General Approach

Separately by cohort, the proportion of evaluable patients who experience a CR will be reported along with a confidence interval; the proportion of patients who experience a PR will also be reported along with a confidence interval.

10.2.2 Analysis of the Primary Efficacy Endpoints

In each of the two cohorts, the fraction of evaluable patients who experience a complete response will be determined and this fraction will be reported along with a 95% confidence interval.

10.2.3 Analysis of the Secondary Efficacy Endpoints

In each of the two cohorts, the fraction of evaluable patients who experience a partial response will be determined and this fraction will be reported along with a 95% confidence interval.

10.2.4 Safety Analyses

Safety of the agent will be assessed by determining the grade of adverse events noted in each patient, and reporting the fraction with grade 3 and grade 4 adverse events. Safety data will be presented in summaries, overall and by cohort. The safety data will consist of the reporting of all adverse events, and may also include reporting vital signs, physical examination data, and laboratory safety data.

10.2.5 Baseline Descriptive Statistics

Limited demographic and clinical characteristics of all patients will be reported.

10.2.6 Planned Interim Analyses

None will be performed.

10.2.7 Subgroup Analyses

Results will be reported according to the cohort in which the patient was enrolled.

10.2.8 Tabulation of Individual Participant Data

No individual participant data is intended to be reported.

10.2.9 Exploratory analyses

Exploratory analyses may include the following:

- Evaluation of PD-L1 and/or TGF-β expression as a potential biomarker of response by comparing levels of their expression between responders (PR +CR) and non-responders, separately within each cohort, using an exact Wilcoxon rank sum test
- Evaluation of HPV type as a potential biomarker of response by determining if the distribution of responders vs. non-responders varies by HPV type using either Fisher's exact test or Mehta's modification to Fisher's exact test, depending on the number of categories of HPV type being evaluated (2 vs. 3)
- Descriptive analyses of induction of HPV-specific T cell responses
- Descriptive analysis of the clearance of HPV infection from normal appearing mucosa
- Determination of the effect of treatment with M7824 on Derkay and Voice Handicap Index-10 scores relative to pre-treatment levels using paired tests such as a Wilcoxon signed rank test
- Determination of the duration of clinical responses to M7824 beginning at the date that a clinical response has been identified, using the Kaplan-Meier method

11 COLLABORATIVE AGREEMENT

11.1 COOPERATIVE RESEARCH AND DEVELOPMENT AGREEMENT

- The study drug M7824 will be provided under a CRADA (EMD Serono, Inc – NCI CRADA# 02666) between the manufacturer, EMD Serono, and the Center for Cancer Research, National Cancer Institute

12 HUMAN SUBJECTS PROTECTIONS

12.1 RATIONALE FOR SUBJECT SELECTION

The patients to be entered in this protocol have RRP involving multiple anatomic sites and requiring repeated procedures for disease control. There is no curative therapy for these patients and their disease causes substantial morbidity and occasional mortality. Subjects from both genders and all racial/ethnic groups are eligible for this study if they meet the eligibility criteria. To date, there is no information that suggests that differences in disease response would be expected in one group compared to another. Efforts will be made to extend accrual to a representative population, but in this preliminary study, a balance must be struck between patient safety considerations and limitations on the number of individuals exposed to potentially toxic and/or ineffective treatments on the one hand and the need to explore gender and ethnic aspects of clinical research on the other hand. If differences in outcome that correlate to gender or to ethnic identity are noted, accrual may be expanded or a follow-up study may be written to investigate those differences more fully.

There is no effective systemic therapy for patients with RRP.

RRP causes death by airway compromise, mass effect in the lungs, and transformation into invasive cancer.

12.2 STRATEGIES/PROCEDURES FOR RECRUITMENT

Patients for this protocol will be recruited via standard CCR mechanisms as well as various advertising venues. All advertisements, letters and other recruitment efforts will be submitted to the IRB for approval prior to their implementation.

12.3 PARTICIPATION OF CHILDREN

Because no dosing or adverse event data are currently available on the use of M7824 in patients <18 years of age, children are excluded from this study, but will be eligible for future pediatric trials.

12.4 PARTICIPATION OF PREGNANT WOMEN

Based on its mechanism of action and data from animal studies, M7824 can cause fetal harm when administered to a pregnant woman. Human IgG1 is known to cross the placental barrier and M7824 is an immunoglobulin G1 (IgG1); therefore, M7824 has the potential to be transmitted from the mother to the developing fetus. Given these risks, pregnant women will be excluded from this study and patients of both genders must be willing to practice contraception throughout M7824 treatment and for at least 120 days after M7824 treatment.

12.5 EVALUATION OF BENEFITS AND RISKS/DISCOMFORTS

The experimental treatment has a chance to provide clinical benefit though this is unknown. The safety profile of M7824 has been established in treatment of over 500 patients. The risks are well-characterized and the toxicities are generally reversible. RRP carries the risk of repeated procedures to control the disease and the potential for airway compromise, lung compression and infection, and transformation to invasive cancer. If this study has a positive outcome it will provide benefit to not only the patients on the study but also to future patients. This study may

also contribute to our knowledge of the mechanism of action of M7824 and the biology or RRP that will help to advance treatment of RRP and other diseases.

12.5.1 Summary of risks and potential benefits

This clinical trial is being performed to evaluate M7824 for RRP. Only patients with a substantial disease burden (Derkay anatomic score of 10 or greater) that requires repeated endoscopic interventions (two or more procedures in the last 12 months) will be eligible for treatment. While the vast majority of patients with RRP experience an acceptable level of disease control with infrequent surgical debulking, a small subset of patients have very aggressive disease that requires frequent operative intervention, carries the risk of airway obstruction and the need for a tracheostomy, and affects their voice and breathing to a degree that negatively impacts their quality of life. The inclusion criteria for this study captures these 5-10% of patients most severely affected. Patients with disease that has not met this level of severity will not be subjected to the risks of treatment. The primary protocol risks are the toxicities of M7824. There may be additional risks of treatment that are specific to RRP such as swelling or progression of papillomas that may lead to worsening symptoms. In addition, there are risks from the general anesthesia and procedures to stage and monitor the disease. General anesthesia will be employed during an initial evaluation to stage the disease, confirm the diagnosis, and debulk papillomas that pose an undue safety risk. It will be used again two weeks after the initiation of treatment at which time the airway will be assessed for safety. A final procedure under anesthesia will be performed at the completion of treatment to remove residual papillomas if they are present. Rare but serious complications can occur with general anesthesia including cardiopulmonary compromise, stroke, and death. In this protocol they are offset substantially by the important safety information related to airway patency, extent of disease, and in some cases surgical removal of disease that is gained by these procedures.

12.5.2 Study drug risks

The risks associated with the study product are discussed in Section **11.1.3**.

12.5.3 Exam under anesthesia and biopsy risks

Exam under anesthesia (EUA) is associated with the risk of sedation or general anesthesia. Complications of general anesthesia are rare. Serious risks include allergic reaction to a drug, loss of airway control and ventilation, and cardiovascular complications such as hypotension, dysrhythmia, or myocardial infarction, and neurological complications such as stroke or brain damage. The risks associated with biopsies are pain and bleeding at the biopsy site. Rarely, there is a risk of infection at the biopsy site. The anesthesia and biopsies of the initial evaluation have the benefit of confirming the diagnosis and the extent of the disease, and permitting debulking of disease that poses a major airway risk. Similarly, the anesthesia and biopsies at the completion of treatment will either confirm a complete response or will be performed in association with papilloma debulking according to standard of care therapy.

12.5.4 Risks associated with blood sampling

Side effects of blood draws include pain and bruising, lightheadedness, and rarely, fainting.

12.5.5 Risks associated with leukapheresis

Risks may involve bleeding at the apheresis site and lightheadedness. Decrease in blood pressure is considered a less common risk.

12.5.6 Risks associated with intravenous catheter

12.5.7 The risks of IV insertion include temporary pain and bleeding or bruising at the site where the IV enters the skin. In placing the IV, there is a small chance of fluid leaking into the tissue surrounding the IV and infection, which may cause some swelling and discomfort. Rarely, the IV site may become infected, which might require treatment with antibiotics.Risks associated with flexible nasopharyngolaryngoscopy

Complications are very uncommon; but may include tearing, gagging, coughing, and, less frequently, nose bleeding due to the scope being passed through the nose.

12.6 Consent Process and Documentation

The informed consent document will be provided to the participant for review prior to consenting. A designated study investigator will carefully explain the procedures and tests involved in this study, and the associated risks, discomforts and benefits. In order to minimize potential coercion, as much time as is needed to review the document will be given, including an opportunity to discuss it with friends, family members and/or other advisors, and to ask questions of any designated study investigator. A signed informed consent document will be obtained prior to entry onto the study.

The initial consent process as well as re-consent, when required, may take place in person or remotely (e.g., via telephone or other NIH approved remote platforms) per discretion of the designated study investigator and with the agreement of the participant. Whether in person or remote, the privacy of the subject will be maintained. Consenting investigators (and participant, when in person) will be located in a private area (e.g., clinic consult room). When consent is conducted remotely, the participant will be informed of the private nature of the discussion and will be encouraged to relocate to a more private setting if needed.

13 REGULATORY AND OPERATIONAL CONSIDERATIONS

13.1 Study Discontinuation and Closure

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to <study participants, investigator, funding agency, the Investigational New Drug (IND) or Investigational Device Exemption (IDE) sponsor and regulatory authorities>. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping

- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB and as applicable, Food and Drug Administration (FDA).

13.2 Quality Assurance and Quality Control

Each clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion. An individualized quality management plan will be developed to describe a site's quality management.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

13.3 Conflict of Interest Policy

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the National Cancer Institute has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

13.4 Confidentiality and Privacy

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s). This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), and/or regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at the/each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the NCI CCR. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by the clinical site(s) and by NCI CCR research staff will be secured and password protected. At the end of the study, all study databases will be archived at the NCI CCR.

To further protect the privacy of study participants, a Certificate of Confidentiality has been issued by the National Institutes of Health (NIH). This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research participants, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to participants.

14 PHARMACEUTICAL INFORMATION

14.1 DESCRIPTION OF THE INVESTIGATIONAL PRODUCT (IND: 138835)

M7824 drug product will be supplied by EMD Serono as a sterile liquid formulation.

Each vial of Powder for Concentrate for Solution for Infusion (freeze-dried formulation) is packaged in United States Pharmacopeia (USP) and European Pharmacopeia (Ph Eur) type I glass vials. Each vial is filled with 45 mg of M7824 (45 mg/vial) as preservative-free powder containing histidine, trehalose dihydrate, sodium chloride, L-methionine and polysorbate 20 (Tween 20). The vials are closed with a rubber stopper in lyophilization format complying with USP and Ph Eur and sealed with an aluminum plastic crimping cap. Only excipients that conform to the current USP and / or Ph Eur are used for M7824 drug product.

The Concentrate for Solution for Infusion (liquid formulation) is packaged at a 10 mg/mL concentration in USP / Ph Eur type I 50R vials that are filled with drug product solution to allow an extractable volume of 60 mL (600 mg/60 mL). The liquid formulation contains histidine, trehalose dihydrate, sodium chloride, L-methionine and polysorbate 20 (Tween 20). The vials are closed with rubber stoppers within serum format complying with USP and Ph Eur with an aluminum crimp seal closure.

The liquid formulation has the same composition in terms of excipients, qualitatively and quantitatively, except for the addition of water compared with the freeze-dried formulation, which was initially used in the ongoing Phase I study (EMR200647-001). Of note, there is no change to the drug substance process.

For applications in clinical studies, the liquid formulation is diluted directly with 0.9% saline solution (sodium chloride injection) supplied in an infusion bag.

The estimated volumes of delivery are anticipated to be no more than 250 mL, which are clinically acceptable. Detailed information on infusion preparation and administration are provided in the protocol and manual of preparation.

14.1.1 Mode of Action

M7824 is a conjugate comprised of avelumab and the soluble extracellular domain of human TGF-β receptor II (TGF-βRII). Avelumab targets the programmed death–ligand 1 (PD-L1). PD-1 is a negative regulatory receptor expressed by activated T and B lymphocytes. Binding of PD-1 to its ligand, PD-L1, results in the down-regulation of lymphocyte activation. Avelumab inhibits the binding of PD-1 to PD-L1. Inhibition of the interaction between PD-1 and PD-L1 promotes immune responses and antigen-specific T-cell responses to both foreign antigens as well as self-antigens. The "TGF-β trap" portion of the compound sequesters bioavailable TGF-β from the papilloma microenvironment.

14.1.2 Source

M7824 is an investigational agent that will be supplied to the NIH Pharmacy by EMD Serono.

14.1.3 Toxicities

The important potential risks include hypersensitivity, irAEs/autoimmune disorders, anemia, rash with hyperkeratosis/keratoacanthomas/SCC of the skin, embryo-fetal toxicity, and alterations in wound healing or repair of tissue damage.

In addition, after discussion among NCI investigators on multiple protocols using M7824, multiple bleeding events ranging from low grade gingival bleeding and epistaxis to more serious hemoptysis, GI bleeding and hematuria have been observed. Some of these events can be attributed to bleeding events related to cancer directly and others bleeding events can be attributed to colitis or cystitis which is a known toxicity of anti-PD-L1 agents including M7824. However, there remains the possibility that M7824 may increase the overall risk of bleeding in ways that may not be directly related to direct tumor bleeding or inflammatory bleeding events described with checkpoint inhibitors like M7824. It is hypothesized that this possible increased bleeding risk may be due to TGF beta inhibition which has an effect on angiogenesis; bleeding has also been observed in patients receiving M7824 and may be drug-related (e.g., gum bleeding, nose bleeds, coughing up blood, blood in their urine, or blood in the stool). Accordingly, patients will be notified of the same possible risk in the informed consent document for this study.

14.1.4 Preparation

M7824 drug product must be diluted in 250 mL of 0.45% or 0.9% saline solution (sodium chloride injection) supplied in an infusion bag. Detailed information on infusion bags and

medical devices to be used for the preparation of the dilutions and subsequent administration will be provided in the manual of preparation.

Prior to the preparation of the dilution for final infusion, allow each vial to equilibrate to room temperature. Use a disposable syringe equipped with a needle of suitable size to remove a volume of sodium chloride solution to be replaced by M7824 from the infusion bag and discard the removed solution. Use a new disposable syringe equipped with a needle of suitable size to inject a volume of M7824 drug product identical to the discarded volume of sodium chloride solution into the infusion bag. Gently invert the mixture 10 times. Infusion bags must not be shaken, in order to avoid foaming or excessive shearing of the protein solution. The preparation must be carefully inspected as it should result in a homogeneous looking clear solution, free of visible particles.

14.1.5 Storage and Stability

M7824 drug product must be stored at 2°C to 8°C until use, and it must not be frozen. Rough shaking of M7824 product must be avoided. M7824 drug product must be diluted with 0.45% or 0.9% saline solution. It is recommended that the diluted M7824 solution is used immediately.

14.1.6 Administration procedures

Please see section **3.2.1**.

14.1.7 Potential Drug Interactions

No formal drug interaction trials have been conducted with M7824 in humans.

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16 APPENDICES

16.1 APPENDIX A: PERFORMANCE STATUS CRITERIA(33)

ECOG Performance Status Scale*	
Grade	Descriptions
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.

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16.2 APPENDIX B: VOICE HANDICAP INDEX-10 (34, 35)

	Never 0	Almost never 1	Sometimes 2	Almost always 3	Always 4
My voice makes it difficult for people to hear me					
People have difficulty understanding me in a noisy room					
People ask "what's wrong with your voice?"					
I feel as though I have to strain to produce voice					
My voice difficulties restrict personal and social life					
The clarity of my voice is unpredictable					
I feel left out of conversations because of my voice					
My voice problem causes me to lose income					
My voice problem upsets me					
My voice makes me feel handicapped					

Total Score:_____

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16.3 APPENDIX C: MANAGEMENT OF IMMUNE-RELATED ADVERSE EVENTS

Immune-Related Adverse Events

Since inhibition of PD-L1 stimulates the immune system, immune-related AEs (irAEs) may occur. Treatment of irAEs is mainly dependent upon severity (NCI-CTCAE grade):

Grade 1 to 2: treat symptomatically or with moderate dose steroids, more frequent monitoring

Grade 1 to 2 (persistent): manage similar to high grade AE (Grade 3 to 4)

Grade 3 to 4: treat with high dose corticosteroids

16.3.1 Gastrointestinal irAEs

Gastrointestinal irAEs		
Severity of Diarrhea / Colitis (NCI-CTCAE v5)	**Management**	**Follow-up**
Grade 1 Diarrhea: < 4 stools/day over Baseline Colitis: asymptomatic	Continue M7824 therapy Symptomatic treatment (for example, loperamide)	Close monitoring for worsening symptoms Educate subject to report worsening immediately If worsens: Treat as Grade 2 or 3/4
Grade 2 Diarrhea: 4 to 6 stools per day over Baseline; IV fluids indicated < 24 hours; not interfering with ADL Colitis: abdominal pain; blood in stool	Delay M7824 therapy Symptomatic treatment	If improves to Grade 1: Resume M7824 therapy If persists > 5 to 7 days or recur: 0.5 to 1.0 mg/kg/day methylprednisolone or equivalent When symptoms improve to Grade 1, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume M7824 therapy per protocol. If worsens or persists > 3 to 5 days with oral steroids: Treat as Grade 3 to 4
Grade 3 to 4 Diarrhea (Grade 3): ≥ 7 stools per day over Baseline; incontinence; IV fluids ≥ 24 hrs; interfering with ADL Colitis (Grade 3): severe abdominal pain, medical intervention indicated, peritoneal signs Grade 4: life-threatening, perforation	Discontinue M7824 therapy per protocol 1.0 to 2.0 mg/kg/day methylprednisolone IV or equivalent Add prophylactic antibiotics for opportunistic infections Consider lower endoscopy	If improves: Continue steroids until Grade 1, then taper over at least 1 month If persists > 3 to 5 days, or recurs after improvement: Add infliximab 5 mg/kg (if no contraindication), Note: Infliximab should not be used in cases of perforation or sepsis

16.3.2 Dermatological AEs

Dermatological AEs		
Grade of Rash (NCI-CTCAE v5)	**Management**	**Follow-up**
Grade 1 to 2 Covering ≤ 30% body surface area	Symptomatic therapy (for example, antihistamines, topical steroids) Continue M7824 therapy	If persists > 1 to 2 weeks or recurs: Consider skin biopsy Delay M7824 therapy Consider 0.5 to 1.0 mg/kg/day methylprednisolone IV or oral equivalent. Once improving, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume M7824 therapy If worsens: Treat as Grade 3 to 4
Grade 3 to 4 Covering > 30% body surface area; life threatening consequences	Delay or discontinue M7824 therapy Consider skin biopsy Dermatology consult 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent	If improves to Grade 1: Taper steroids over at least 1 month and add prophylactic antibiotics for opportunistic infections Resume M7824 therapy

16.3.3 Pulmonary AEs

Pulmonary AEs		
Grade of Pneumonitis (NCI-CTCAE v5)	**Management**	**Follow-up**
Grade 1 Radiographic changes only	Consider delay of M7824 therapy Monitor for symptoms every 2 to 3 days Consider Pulmonary and Infectious Disease consults	Re-image at least every 3 weeks If worsens: Treat as Grade 2 or Grade 3 to 4
Grade 2 Mild to moderate new symptoms	Delay M7824 therapy Pulmonary and Infectious Disease consults Monitor symptoms daily, consider hospitalization 1.0 mg/kg/day methyl-prednisolone IV or oral equivalent Consider bronchoscopy, lung biopsy	Re-image every 1 to 3 days If improves: When symptoms return to near Baseline, taper steroids over at least 1 month and then resume M7824 therapy and consider prophylactic antibiotics If not improving after 2 weeks or worsening: Treat as Grade 3 to 4
Grade 3 to 4 Severe new symptoms; New / worsening hypoxia; life-threatening	Discontinue M7824therapy Hospitalize Pulmonary and Infectious Disease consults 2 to 4 mg/kg/day methylprednisolone IV or IV equivalent Add prophylactic antibiotics for opportunistic infections Consider bronchoscopy, lung biopsy	If improves to Baseline: Taper steroids over at least 6 weeks If not improving after 48 hours or worsening: Add additional immunosuppression (for example, infliximab, cyclophosphamide, IV immunoglobulin, or mycophenolate mofetil)

16.3.4 Hepatic AEs

Hepatic AEs		
Grade of Liver Test Elevation (NCI-CTCAE v5)	**Management**	**Follow-up**
Grade 1 Grade 1 AST or ALT > ULN to 3.0 x ULN and / or total bilirubin > ULN to 1.5 x ULN	Continue M7824 therapy	Continue liver function monitoring If worsens: Treat as Grade 2 or 3 to 4
Grade 2 AST or ALT > 3.0 to ≤ 5 x ULN and / or total bilirubin > 1.5 to ≤ 3 x ULN	Delay M7824therapy Increase frequency of monitoring to every 3 days	If returns to Baseline: Resume routine monitoring, resume M7824 therapy If elevations persist > 5 to 7 days or worsen: 0.5 to 1 mg/kg/day methylprednisolone or oral equivalent and when LFT returns to Grade 1 or Baseline, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume M7824 therapy
Grade 3 to 4 AST or ALT > 5 x ULN and / or total bilirubin > 3 x ULN	Discontinue M7824 therapy Increase frequency of monitoring to every 1 to 2 days 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent Add prophylactic antibiotics for opportunistic infections Consult gastroenterologist Consider obtaining MRI/CT scan of liver and liver biopsy if clinically warranted	If returns to Grade 2: Taper steroids over at least 1 month If does not improve in > 3 to 5 days, worsens or rebounds: Add mycophenolate mofetil 1 gram (g) twice daily If no response within an additional 3 to 5 days, consider other immunosuppressants per local guidelines

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16.3.5 Cardiac AEs

Cardiac irAEs		
Myocarditis	**Management**	**Follow-up**
New onset of cardiac signs or symptoms and / or new laboratory cardiac biomarker elevations (e.g. troponin, CK-MB, BNP) or cardiac imaging abnormalities suggestive of myocarditis.	Withhold M7824 therapy Hospitalize. In the presence of life threatening cardiac decompensation, consider transfer to a facility experienced in advanced heart failure and arrhythmia management. Cardiology consult to establish etiology and rule-out immune-mediated myocarditis. Guideline based supportive treatment as per cardiology consult.* Consider myocardial biopsy if recommended per cardiology consult.	If symptoms improve and immune-mediated etiology is ruled out, re-start M7824 therapy. If symptoms do not improve/worsen, viral myocarditis is excluded, and immune-mediated etiology is suspected or confirmed following cardiology consult, manage as immune-mediated myocarditis.
Immune-mediated myocarditis	Permanently discontinue M7824. Guideline based supportive treatment as appropriate as per cardiology consult.* Methylprednisolone 1 to 2 mg/kg/day.	Once improving, taper steroids over at least 1 month and add prophylactic antibiotics for opportunistic infections. If no improvement or worsening, consider additional immunosuppressants (e.g. azathioprine, cyclosporine A)
*Local guidelines, or eg. ESC or AHA guidelines ESC guidelines website: https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines AHA guidelines website: http://professional.heart.org/professional/GuidelinesStatements/searchresults.jsp?q=&y=&t=1001		

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16.3.6 Endocrine AEs

Endocrine AEs		
Endocrine Disorder	**Management**	**Follow-up**
Asymptomatic TSH abnormality	Continue M7824 therapy If TSH < 0.5 x LLN, or TSH > 2 x ULN, or consistently out of range in 2 subsequent measurements: include T4 at subsequent cycles as clinically indicated; consider endocrinology consult	
Symptomatic endocrinopathy	Evaluate endocrine function Consider pituitary scan Symptomatic with abnormal lab / pituitary scan: Delay M7824 therapy 1 to 2 mg/kg/day methylprednisolone IV or by mouth equivalent Initiate appropriate hormone therapy No abnormal lab / pituitary MRI scan but symptoms persist: Repeat labs in 1 to 3 weeks / MRI in 1 month	If improves (with or without hormone replacement): Taper steroids over at least 1 month and consider prophylactic antibiotics for opportunistic infections Resume M7824 therapy Subjects with adrenal insufficiency may need to continue steroids with mineralocorticoid component
Suspicion of adrenal crisis (for example, severe dehydration, hypotension, shock out of proportion to current illness)	Delay or discontinue M7824 therapy Rule out sepsis Stress dose of IV steroids with mineralocorticoid activity IV fluids Consult endocrinologist If adrenal crisis ruled out, then treat as above for symptomatic endocrinopathy	

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16.4 APPENDIX D: DERKAY STAGING FOR RRP

STAGING ASSESSMENT FOR RECURRENT LARYNGEAL PAPILLOMATOSIS

PATIENT INITIALS:_____ DATE OF SURGERY_____ SURGEON_____
PATIENT ID #_____ INSTITUTION_____

1. How long since the last papilloma surgery? _____days, ____weeks, ____months,
   ____years,____ don't know,
   _____this is the child's first surgery
2. Counting today's surgery, how many papilloma surgeries in the past 12 months? _____
3. Describe the patient's voice today:
   normal__(0), abnormal__(1), aphonic__(2)
4. Describe the patient's stridor today:
   absent__(0), present with activity__(1), present at rest__(2)
5. Describe the urgency of today's intervention:
   scheduled__(0),elective__(1),urgent__(2),emergent(3)
6. Describe today's level of respiratory distress:
   none__(0), mild__(1), Mod__(2), severe__(3), extreme__(4)

Total score for questions 3-6=_____

FOR EACH SITE, SCORE AS: 0= NONE, 1= SURFACE LESION, 2=RAISED LESION, 3=BULKY LESION

LARYNX:
- Epiglottis
  - Lingual surface_____ Laryngeal surface_____
- Aryepiglottic folds: Right____ Left_____
- False vocal cords: Right____ Left_____
- True vocal cords: Right____ Left_____
- Arytenoids: Right_____ Left_____
- Anterior commissure_____
- Posterior commissure_____
- Subglottis _____

TRACHEA:
- Upper one-third_____
- Middle one-third_____
- Lower one-third_____
- Bronchi: Right____ Left_____
- Tracheotomy stoma_____

OTHER:
- Nose_____
- Palate_____
- Pharynx_____
- Esophagus_____
- Lungs_____
- Other_____

TOTAL SCORE ALL SITES: _____ TOTAL CLINICAL SCORE:_____

Fig. 1. Staging/severity scale.

The anatomic score will be used to determine response or progression-see section **6.2**