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

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F. Studying, interpreting, or analyzing de-identified data or specimens for research purposes
G. Some/all research activities performed outside NIH

Investigational Agent:

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Avelumab</th>
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<tr>
<td>IND Number</td>
<td>130884</td>
</tr>
<tr>
<td>Sponsor</td>
<td>Center for Cancer Research</td>
</tr>
<tr>
<td>Manufacturer</td>
<td>EMD Serono</td>
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Commercial Agents: None
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 require repeated interventional procedures for disease control.
- Study of a small number of RRP samples has shown PD-L1 expression by inflammatory mononuclear cells and by papilloma epithelial cells.
- This clinical trial will evaluate the activity of a PD-L1-targeted drug, avelumab, in the treatment of RRP. 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 avelumab 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

- Phase II clinical trial
- Simon optimal two-stage design with initial enrollment of 12 patients and expansion to 37 patients if one or more complete response(s) is/are observed in the initial patients.
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1 INTRODUCTION

1.1 STUDY OBJECTIVES

1.1.1 Primary Objective

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

1.1.2 Secondary Objectives

- Exploratory analyses to assess:
  - PD-L1 expression as a potential biomarker of response.
  - HPV type as a potential biomarker of response.
  - Induction of HPV-specific T cells responses.
  - Clearance of HPV infection from normal appearing mucosa.

- Determine the effect of treatment with avelumab on Derkay and Voice Handicap Index-10 scores.

- Determine the partial response rate for avelumab

- Determine the duration of clinical responses to avelumab

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 persistent 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.

1.2.2 Avelumab

Avelumab is a fully human monoclonal antibody (HuMAb; immunoglobulin G1 [IgG1]) that targets programmed death-ligand 1 (PD-L1). Programmed death-1 (PD-1) is a negative regulatory molecule expressed by activated T and B lymphocytes. Binding of PD-1 to its ligand, PD-L1, results in the down-regulation of lymphocyte activation (Figure 1). Inhibition of the interaction between PD-1 and PD-L1 promotes activation of adaptive immunity and antigen-specific T-cell responses to both foreign antigens as well as self-antigens. Avelumab is produced using standard mammalian cell cultivation and chromatographic purification technologies.

The clinical use of monoclonal antibodies that block T-cell inhibitory receptors has provided transformative information on the nature of the immune system and cancer. An emerging picture suggests that endogenous immune responses can mediate effective tumor regression and/or improved survival even in patients with large volume tumors resistant to other forms of therapy. Some of the unique features of this type of therapy, based largely on experience in advanced melanoma, include: improved overall survival (OS) with or without radiographic responses or improved progression-free survival (PFS); responses that may be delayed or occur after radiographic disease progression; combinations of immune modulators with enhanced or novel activities (in the example of anti-CTLA4 and anti-PD-1 agents); and toxicity that is almost
exclusively immune or inflammatory in nature. It is not yet clear what factors determine responses and which components of the immune system are needed for this to occur. It seems likely that both memory helper and effector cells would be needed to sustain long-term responses. Increasing emphasis has been placed on understanding the relationships of the tumor, cellular infiltrate, and immunologic milieu surrounding each tumor.

PD-1, a 55-kDa type 1 transmembrane protein, is a member of the CD28 family of T-cell co-stimulatory receptors that include Ig super family member CD28, CTLA-4, inducible co-stimulator (ICOS), and B and T lymphocyte attenuator (BTLA).[8] PD-1 is transiently but highly expressed on activated T cells functioning to limit immune effectors at the site of activation. Chronic stimulation may prevent the re-methylation of the PD-1 gene leading to continuous expression and characterizes a state of “exhausted” T cells that lose function and proliferative capacity while enhancing a suppressive tumor microenvironment. PD-1 may act together with other T-cell modulating molecules, including CTLA-4, TIM-3, lymphocyte-activation gene 3 (LAG-3) as well as indoleamine-pyrrole 2,3-dioxygenase 1 (IDO-1), cytokines, and transforming growth factor beta (TGF-beta).

Two ligands specific for PD-1 have been identified: PD-ligand 1 (PD-L1, also known as B7-H1 or CD274, expressed on tumor, antigen-presenting cells [APCs], and dendritic cells [DCs]) and PD-L2 (also known as B7-DC or CD273, expressed on endothelial cells). The interaction of PD-1 with PD-L1 and PD-L2 results in negative regulatory stimuli that down-modulate the activated T-cell immune response through SHP-1 phosphatase.

PD-1 knockout mice develop strain-specific lupus-like glomerulonephritis (C57BL/6) and cardiomyopathy (BALB/c). In transplantable tumor models that expressed PD-1 and LAG-3 on tumor-infiltrating CD4⁺ and CD8⁺ T cells dual anti-LAG-3/anti-PD-1 antibody treatment cured most mice of established tumors that were largely resistant to single antibody treatment.[9] Despite minimal immunopathologic sequelae in PD-1 and LAG-3 single knockout mice, dual knockout mice abrogated self-tolerance with resultant autoimmune infiltrates in multiple organs, leading to eventual lethality.


The PD-1/PD-L1 axis plays a role in human infections, particularly in hepatitis C virus (HCV) and human immunodeficiency virus (HIV). In these cases, high expression levels of PD-1 were found in viral-specific CD8⁺ T cells that also display a non-responsive or exhausted phenotype. Non-responsive PD-1-high T cells were observed in simian immunodeficiency virus (SIV) infection in rhesus macaques. Treatment of SIV-infected macaques with an anti-PD-1 mAb (3 mg/kg x 4) resulted in decreased viral loads and increased survival along with expanded T cells with increased T-cell functionality.

1.2.2.1 Nonclinical Development of Avelumab

In intravenous (IV) repeat-dose toxicology studies in cynomolgus monkeys, avelumab alone was well tolerated (change this reference to the avelumab IB)[8]. Avelumab bound specifically to monkey PD-L1 with an affinity constant of 1.1 nM. In monkeys, a no-observed-adverse-effect-level was observed at a dose of avelumab significantly higher (140 mg/ml) than that selected for
Clinical development (10 mg/ml). Avelumab monotherapy increased survival time in MC38 (colon carcinoma) and PANC02 (pancreas adenocarcinoma) tumor-bearing mice in a CD8 T-cell dependent fashion and appeared to induce NK-cell mediated antibody dependent cellular cytotoxicity in some tumors.

1.2.2.2 Clinical Development of avelumab

Avelumab is an investigational fully-human monoclonal antibody (IgG1) that specifically targets PD-L1. It has demonstrated clinical activity in a variety of solid tumor types including NSCLC, merkel-cell carcinoma, gastric, ovarian and bladder cancer. Similar to other checkpoint inhibitors, many responses have been durable lasting beyond the duration of active therapy. Over 700 patients have been treated in initial MTD and expansion cohort phase I trials, with a phase II trial in metastatic merkel-cell carcinoma and a phase III trial in recurrent NSCLC underway. The clinical activity and safety information presented here focuses primarily on data obtained from EMR100070-001 (Phase I, open label trial in primarily Caucasian patients) and MER100070-002 (Phase I, open label trial in Asian patients).

Nine of 53 (16.9%) initial patients experienced ≥ grade 3 AEs potentially related to avelumab including immune-related AEs. None of the subjects treated with doses up to 10 mg/kg experienced a DLT, thus 10 mg/kg q2 weeks dose of avelumab was considered a safe and well-tolerated dose for further investigation in the expansion cohorts.

Expansion cohorts in breast, NSCL, gastric, ovarian and urothelial cancer were administered 10 mg/kg every 2 weeks. Of 717 patients treated with this dose and schedule, 498/717 (69%) experienced treatment-related AEs of any grade and 77/717 (10.7%) experienced ≥ grade 3 AEs. The most common grade 3 reactions included infusion side related reactions, (134, 18.7%), fatigue (130, 18.1%), nausea (74, 10.3%), diarrhea (49, 6.8%), chills (48, 6.7%), and decreased appetite (37, 5.2%). The 14 subjects reporting Grade 4 treatment-related TEAEs included 7 subjects (3.8%) in the NSCL expansion cohort with the PTs of infusion-related reaction (2 subjects), amylase increased, embolic stroke, frontal lobe epilepsy, monoplegia, syncope, dyspnea, pneumonitis, and autoimmune neutropenia (each in 1 subject). Further Grade 4 treatment-related TEAEs were seen in 5 subjects of the metastatic breast cancer (MBC) expansion cohort (3.0%) with the PTs of gamma-glutamyltransferase increased, hypokalemia, respiratory failure, anemia, neutropenia, thrombocytopenia, and cardiac arrest (each in 1 subject). The other 2 subjects who reported Grade 4 treatment-related TEAEs were 1 subject in the mesothelioma expansion cohort (blood creatine phosphokinase increased) and 1 subject in the urothelial carcinoma expansion cohort (myositis).

The 4 subjects who experienced Grade 5 treatment-related TEAEs were 2 subjects in the NSCLC expansion cohort (radiation pneumonitis [Subject ID 172-0004] and acute respiratory failure [Subject ID: 168-0004]) and 2 subjects in the MBC expansion cohort (respiratory distress [Subject ID 139-0004] and acute hepatic failure [Subject ID: 120-0014]).

The NSCLC and ovarian carcinoma expansion cohorts from the EMR100070-001 trial have demonstrated objective response rates of 13.6% and 10.7%, respectively. Within the NSCLC expansion cohort, progression free survival was extended from 5.9 weeks to 12 weeks and overall survival was extended from 4.6 months to 8.9 months.
1.2.2.3 Pharmacokinetics

Pharmacokinetics (PK) of avelumab was linear in the range of 1 to 20 mg/kg, with dose-proportional increases in maximum serum concentration (C_{max}) and area under the concentration-time curve from time zero to infinity (AUC_{0-∞}), with low to moderate inter-subject variability observed at each dose level. Clearance of avelumab is independent of dose in the dose range (1-20 mg/kg). Body weight normalized dosing showed approximately constant trough concentrations over a wide range of body weights. The mean terminal elimination half-life of avelumab is 5 days.

1.2.3 PD-1-targeted therapy for RRP

RRP is caused by HPV infection. HPV infections are common, but most individuals clear the virus without manifesting papillomas, dysplasia, or invasive cancers. 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. 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.

Clinical trials with new immunotherapeutic agents such as checkpoint inhibitors that block the cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), or programmed cell death 1 (PD-1) receptors or their ligands such as PD-L1, have not been reported for the treatment of RRP. PD-1 expression has been observed by flow cytometric analysis of T cells infiltrating respiratory papillomas, and PD-L1 mRNA expression in papillomas has been observed by RT-PCR. Expression of PD-L1 by tumor-infiltrating immune cells or by the tumor cells themselves has positively correlated with tumor response in clinical trials of drugs PD-1/PD-L1-targeted drugs. This clinical trial will evaluate the activity of a PD-L1-targeted drug, avelumab, in the treatment of RRP. This drug was selected for its demonstrated activity in a variety of cancers and for its acceptable safety profile.

### Table 1 PD-L1 expression on RRP

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<th></th>
<th>N (30 samples tested)</th>
<th>%</th>
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<td>Epithelial cell membranous or infiltrating hematopoietic cells</td>
<td>24</td>
<td>80</td>
</tr>
<tr>
<td>Epithelial cell membranous</td>
<td>18</td>
<td>60</td>
</tr>
<tr>
<td>Infiltrating hematopoietic cell</td>
<td>22</td>
<td>73</td>
</tr>
<tr>
<td>Epithelial cell membranous and infiltrating hematopoietic cells</td>
<td>16</td>
<td>53</td>
</tr>
</tbody>
</table>
1.2.4 Summary of risks and potential benefits

This clinical trial is being performed to evaluate avelumab 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 avelumab. 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.

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:
  o A Derkay anatomic score of 10 or greater (See Section 12.4) and a history of two or more endoscopic interventions in the last 12 months for control of RRP.
  o Pulmonary RRP with pulmonary disease that is measurable by computed tomography scan.
  o Tracheal involvement with RRP that has required either two or more endoscopic interventions in the last 12 months or a tracheostomy.
• Greater than or equal to 18 years of age.

2.1.1.2 Able to understand and sign the Informed Consent Document.

2.1.1.3 Clinical performance status of ECOG 0 or 1. See section 12.1.

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

2.1.1.5 No systemic therapy for RRP for four weeks prior to treatment.

2.1.1.6 Screening laboratory values must meet the following criteria and should be obtained within 14 days prior to first dose:
  o WBC > 2000/μL
  o Neutrophils > 1500/μL
  o Platelets > 100 x10^3/μL
  o Hemoglobin > 9.0 g/dL
  o Serum creatinine < 1.5 x ULN or creatinine clearance (CrCl) > 30 mL/min (measured or calculated using the Cockcroft-Gault formula below):
    Female CrCl: \[
    \frac{(140 - \text{age in years}) \times \text{weight in kg} \times 0.85}{72 \times \text{serum creatinine in mg/dL}}
    \]
    Male CrCl: \[
    \frac{(140 - \text{age in years}) \times \text{weight in kg} \times 1.00}{72 \times \text{serum creatinine in mg/dL}}
    \]
  o AST/ALT ≤ 2.5 x ULN; for subjects with documented metastatic disease to the liver, AST and ALT levels ≤ 5 × ULN
  o Total Bilirubin ≤ 1.5 x ULN

2.1.1.7 Sexually active subjects (men and women) and all subjects of reproductive potential must agree to use two methods of contraception: one highly effective and one other effective method for at least 28 days prior, throughout the avelumab treatment and for at least 60 days after avelumab 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.
2.1.1.8 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.

2.1.1.9 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.

2.1.1.10 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 Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or immune checkpoint pathways.

2.1.2.6 Patients who are receiving any other investigational agents

2.1.2.7 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.

2.1.2.8 History of allergy to study drug components.

2.1.2.9 History of severe hypersensitivity reaction to any monoclonal antibody (Grade ≥ 3 NCI-CTCAE v 4.03), any history of anaphylaxis, or uncontrolled asthma (that is, 3 or more features of partially controlled asthma).

2.1.2.10 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.

2.1.2.11 Persisting toxicity related to prior therapy of Grade >1 NCI-CTCAE v 4.03; however, alopecia, sensory neuropathy Grade ≤ 2 or other Grade ≤ 2 AEs not constituting a safety risk based on investigator's judgment are acceptable.

2.1.2.12 Known alcohol or drug abuse.

2.1.2.13 Vaccination within 4 weeks of the first dose of avelumab and while on trial is prohibited except for administration of inactivated vaccines.

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 videostroscopy. 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 2.1.1.8 - 2.1.1.10 (within 90 days prior to subject enrollment).
2.2.2 Within 3 days prior to subject receiving the first dose of study drug:

2.2.2.1 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

2.2.2.2 Pregnancy test in women of childbearing potential.

2.2.2.3 Review of concomitant 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 imaging is used for response assessment. For other baseline evaluations please refer to the Study Calendar (Section 3.5).

2.4 REGISTRATION PROCEDURES

Authorized staff must register an eligible candidate with NCI Central Registration Office (CRO) within 24 hours of signing consent. A registration Eligibility Checklist from the web site (http://home.ccr.cancer.gov/intra/eligibility/welcome.htm) must be completed and sent via encrypted email to: NCI Central Registration Office ncicentralregistration-l@mail.nih.gov. After confirmation of eligibility at Central Registration Office, CRO staff will call pharmacy to advise them of the acceptance of the patient on the protocol prior to the release of any investigational agents. Verification of Registration will be forwarded electronically via e-mail to the research team. A recorder is available during non-working hours.

3 STUDY IMPLEMENTATION

3.1 STUDY DESIGN

3.1.1 General study plan

This protocol is a phase II study of avelumab. 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. 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. 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. Leukapheresis will be performed prior to the first dose of avelumab (see Section 4.1.1).

Avelumab will be administered at a flat dose of 10 mg/kg 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 avelumab (9-17 days after the first dose).
Leukapheresis will also be obtained at this time point. These procedures should occur before the second dose of avelumab. Disease response will first be assessed six weeks after the first dose of avelumab (+/- 7 days), which corresponds to the end of the first course (3 doses) of avelumab, 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 avelumab, if applicable. If patients have a complete response or no response, 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 (+/- 7 days). 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.
3.1.2 Protocol Schema

Screening and baseline evaluations including:
Clinic-based examinations, EUA, operative endoscopy, biopsy, and leukapheresis

Avelumab 10 mg/kg IV x 1

2 week EUA, operative endoscopy, biopsy, and Leukapheresis H&P, clinic-based endoscopy, Voice Handicap Index-10 and imaging

Avelumab 10 mg/kg IV x q 2 weeks x 2

6 week response assessment: H&P, clinic-based endoscopy, Voice Handicap Index-10 and imaging
Continue treatment only for a PR

Partial response

Avelumab 10 mg/kg IV every other week for 3 doses (6 weeks)

12 week post treatment evaluation including EUA, operative endoscopy with surgical debulking (if residual disease) or biopsy (if CR).
Response assessment: H&P, clinic-based endoscopy, Voice Handicap Index-10 and imaging

No response or complete response

Treatment discontinuation: EUA, operative endoscopy, biopsy (if CR) or surgical debulking (if NR)
3.2 DRUG ADMINISTRATION

3.2.1 Avelumab

Avelumab will be administered at a dose of 10 mg/kg IV every other week for up to 12 weeks total (6 cycles). All patients will be pre-treated with an antihistamine and acetaminophen 30-60 minutes prior to each dose (for example, 25-50 mg diphenhydramine and 500-650 mg acetaminophen). Avelumab is to be diluted in 250 mL of 0.45% or 0.9% saline solution (sodium chloride injection) and administered as an IV infusion, using a volumetric pump with a 0.2/0.22 micron in-line filter at the protocol-specified dose. It is not to be administered as an IV push or bolus injection.

Avelumab 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.

Avelumab 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

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avelumab</td>
<td>10 mg/kg IV</td>
<td>Day 1 of a 14 day cycle (every other week) for up to 12 weeks total treatment (6 cycles)</td>
</tr>
</tbody>
</table>

Response will be assessed by flexible endoscopy with or without imaging studies before treatment and 6 and 12 weeks after starting treatment.

3.3 ON-STUDY ASSESSMENTS

If doses are delayed, assessments and research studies will be postponed accordingly.

3.3.1 Prior to each dose within 3 days of drug administration

- Targeted physical examination if clinically indicated which may include clinic-based flexible nasopharyngolaryngoscopy and/or tracheoscopy with assignment of a Derkay score if the Derkay score is being used as the primary response assessment
- Vital signs and oxygen saturation at rest and after exertion
- Assess for symptoms of myocarditis (chest pain, shortness of breath, swelling of ankles or feet)
- Pregnancy test in women of childbearing potential
• CBC w/differential, LFTs (ALT, AST, total bilirubin, alkaline phosphatase), BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, LDH, glucose, amylase, lipase, TSH with reflexive Free T4, Free T3
• TBNK
• Adverse events assessment
• Research blood:
  • 6 Cell Preparation Tubes (CPT) (48 mL) will be collected for immunological testing and processed as described in section 4.1.1. Attention Jeremy Rose, Bldg. 10, room 12C216 contact phone: 301-594-5339.
  • 1 Serum Separator Tubes (SST) (8 mL) will be obtained for serum collection and processed as described in section 4.1.1. Attention Jeremy Rose, Bldg. 10, room 12C216 contact phone: 301-594-5339.
• Review of concomitant medications
• Voice Handicap Index-10 assessment questionnaire

3.3.2 Additional studies at a single time point two weeks after the first dose of avelumab
• Leukapheresis (see Section 4.1.1)
• Exam under anesthesia (sedation or general anesthesia) including rigid and/or flexible endoscopy with biopsies to assess disease response, clinical signs of inflammation or airway compromise, and to obtain biopsies for research.

3.3.3 Every 6 week (3 cycles) (+/- 7 days) response assessment (performed at 6 and 12 weeks after first dose of avelumab)
• Interval targeted history and physical.
• Clinic-based flexible nasopharyngolaryngoscopy and/or tracheoscopy. This will include standard bright light endoscopy and videostroboscopy, and assignment of a Derkay score. This endoscopic examination combined with radiographic examination (if radiographically measurable disease is present) will be used to determine response to treatment.
• Voice Handicap Index-10 assessment questionnaire, see Section 12.2.
• Imaging studies if imaging is used for response assessment.

3.3.4 Every 1 week 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) will be assessed.
• Laboratory studies as follows: CBC w/differential, LFTs (ALT, AST, total bilirubin, alkaline phosphatase), BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, LDH, glucose, amylase and lipase.
3.3.5 At completion of treatment

- Targeted physical examination if clinically indicated which may include clinic-based flexible nasopharyngolaryngoscopy and/or tracheoscopy
- Vital signs and oxygen saturation at rest and after exertion
- Symptoms of myocarditis (chest pain, shortness of breath, swelling of ankles or feet) will be assessed
- Pregnancy test in women of childbearing potential
- CBC w/differential, LFTs (ALT, AST, total bilirubin, alkaline phosphatase), BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, LDH, glucose, amylase, lipase, TSH with reflexive Free T4, Free T3
- TBNK
- Adverse events assessment

Research blood:

- 6 CPT tubes (48 mL) will be collected for immunological testing and processed as described in section 4.1.1. Attention Jeremy Rose, Bldg. 10, room 12C216 contact phone: 301-594-5339.
- 1 SST tube (8 mL) will be obtained for serum collection and processed as described in section 4.1.1. Attention Jeremy Rose, Bldg. 10, room 12C216 contact phone: 301-594-5339.

Clinic-based flexible nasopharyngolaryngoscopy and/or tracheoscopy. This will include standard bright light endoscopy and may include videostroboscopy, and assignment of a Derkay score if the Derkay score is being used for response assessment. This endoscopic examination will be used to assess treatment response.

- Imaging studies if imaging is used for response assessment.
- Voice Handicap Index-10 assessment questionnaire.
- Exam under anesthesia (sedation or general anesthesia) including rigid and/or flexible endoscopy with biopsies to perform standard of care papilloma debulking, to obtain biopsies for research and to validate complete response or the presence of persistent disease. These tests will be done 2 and 6 weeks after the first dose of avelumab for all patients. The same tests will be repeated 12 weeks after the first dose for patients that demonstrate a partial response and receive an additional 6 weeks of treatment.

3.3.6 Follow-up studies

- Patients who experience a complete response or partial response will be evaluated every 6 weeks x 3, then every 12 weeks x 3, then every 26 weeks x 2 or until disease progression (+/- 10 days for each time point). After completing the first 2 years’ worth of follow-up clinic visits, patients will be contacted annually (+/- one month)
for patient status, dates of disease recurrence and interventions to treat recurrent disease.

- Patients who do not experience a response to treatment will be contacted annually (+/- one month) to document additional disease recurrence and treatments that they have received.

- Evaluations will include:
  - Interval directed history and physical
  - CBC w/differential, LFTs (ALT, AST, total bilirubin, alkaline phosphatase), BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, LDH, glucose, amylase, lipase, TSH with reflexive Free T4, Free T3
  - TBNK
  - Vital signs and oxygen saturation at rest and after exertion
  - Clinic-based flexible nasopharyngolaryngoscopy and/or tracheoscopy including standard bright light endoscopy and videostroboscopy with assignment of a Derkay score
  - Voice Handicap Index-10 assessment questionnaire.

- Research blood: At each clinic visit and at subsequent time points at the discretion of the patient and the investigators:
  - 6 CPT tubes (48 mL) will be collected for immunological testing and processed as described in section 4.1.1. Attention Jeremy Rose, Bldg. 10, room 12C216 contact phone: 301-594-5339.
  - 1 SST tube (8 mL) will be obtained for serum collection and processed as described in section 4.1.1. Attention Jeremy Rose, Bldg. 10, room 12C216 contact phone: 301-594-5339.

- Adverse events will be followed until return to baseline or stabilization of event.
- Imaging studies if imaging is used for response assessment.
- Patients will be contacted 42 days (+/- 10 days) after the last dose of avelumab to check on patient’s status.

### 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 12.3.
3.4.2 Resuming treatment

Subjects may resume treatment with avelumab 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 Avelumab infusion reactions

Since avelumab 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. All Grade 3 or 4 infusion reactions should be reported within 24 hours to the sponsor and reported as an SAE if criteria are met. Infusion reactions should be graded according to NCI CTCAE (version 4.0) guidelines.

<table>
<thead>
<tr>
<th>NCI-CTCAE Grade</th>
<th>Treatment Modification for Study Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Grade 1 – mild</strong></td>
<td>Remain at bedside and monitor subject until recovery from symptoms.</td>
</tr>
<tr>
<td>Mild transient reaction; infusion interruption not indicated; intervention not indicated.</td>
<td>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.</td>
</tr>
<tr>
<td><strong>Grade 2 – moderate</strong></td>
<td>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.</td>
</tr>
<tr>
<td>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.</td>
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<tr>
<td><strong>Grade 3 or Grade 4 – severe or life-threatening; urgent intervention indicated.</strong> Grade 3: Prolonged (for example, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following</td>
<td>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</td>
</tr>
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</table>
inititl improvement; hospitalization indicated for other clinical sequelae [e.g., renal impairment, pulmonary infiltrates]). Grade 4: (life-threatening; pressor or ventilator support indicated).

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 avelumab 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 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 avelumab IV infusion. Alternative treatments for fever (for example, paracetamol) may be given to subjects at the discretion of the Investigator.

3.4.6 Tumor Lysis Syndrome

In addition, since avelumab 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.
### 3.5 Study Calendar

<table>
<thead>
<tr>
<th>Procedures</th>
<th>Screening</th>
<th>Baseline</th>
<th>Course 1</th>
<th>End of Course 1</th>
<th>Course 2 (if indicated)</th>
<th>Course 3</th>
<th>End of Treatment</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>History and PE[b]</td>
<td>X[^f]</td>
<td>X[^c,e]</td>
<td>X[^c,e]</td>
<td>X[^c]</td>
<td>X[^m]</td>
<td>X[^c]</td>
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<tr>
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<td>CBC with differential</td>
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<td>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[^c]</td>
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<td>X[^c,e]</td>
<td>X[^c,e]</td>
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<td>X[^m]</td>
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<td>Antibody screen for Hepatitis B and C; HIV[^p]</td>
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</table>

\[^a\] End of Treatment \[^a\]

\[^b\] History and PE

\[^c\] Vital signs

\[^d\] ECOG Performance Score

\[^e\] Confirmation of diagnosis

\[^f\] NIH Advance Directives Form

\[^g\] CBC with differential

\[^h\] 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

\[^i\] Antibody screen for Hepatitis B and C; HIV
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<th>Follow-up</th>
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<tbody>
<tr>
<td>Pregnancy test(^c)</td>
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<tr>
<td>Imaging</td>
<td>X(^e,f)</td>
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<td>X(^a,m,n)</td>
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<td>X(^m,n) X(^m,n)</td>
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<td>ECG</td>
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<tr>
<td>Clinic-based Flexible nasopharyngolaryngoscopy and/or tracheoscopy with Derkay score</td>
<td>X(^f)</td>
<td>X(^c,e)</td>
<td>X(^i)</td>
<td>X(^j) X(^k)</td>
<td>X(^c) X(^c) X(^c) X(^c) X(^m) X(*)</td>
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<tr>
<td>Voice Handicap Index-10</td>
<td>X(^c)</td>
<td>X(^c)</td>
<td>X(^c)</td>
<td>X(^c)</td>
<td>X(^c) X(^c) X(^c) X(^c) X(*)</td>
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<tr>
<td>Exam under anesthesia with biopsies and possible debulking</td>
<td>X(^h)</td>
<td>X(^i)</td>
<td>X(^k)</td>
<td></td>
<td></td>
<td>X(^l)</td>
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<td>Research Blood(^c)</td>
<td>X(^c)</td>
<td>X(^c)</td>
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<td>X(^c)</td>
<td>X(^c) X(^c) X(^c) X(^c) X(*)</td>
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<tr>
<td>Adverse Events(^c)</td>
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<td>X(^c)</td>
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<td>X(^c) X(^c) X(^c) X(^c) X(*)</td>
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<tr>
<td>Concomitant Medications(^c)</td>
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<td>X(^c)</td>
<td>X(^c)</td>
<td>X(^c)</td>
<td>X(^c) X(^c) X(^c) X(^c) X(*)</td>
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<td>Leukapheresis</td>
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<tr>
<td>Avelumab</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
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</tr>
</tbody>
</table>

\(^a\) End of Treatment studies will be performed 42 days (+/- 10 days) after the final Avelumab 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 procedures must be performed within 3 days before each dose of avelumab while on treatment.
d Adverse events will be followed until return to baseline or stabilization of event.

c If the screening and baseline tests were performed prior to 3 days before the first dose of avelumab 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 avelumab

i 9-17 days after first dose of avelumab and before second dose of avelumab

j 9-17 days after second dose of avelumab and before third dose of avelumab

k 9-17 days after third dose of avelumab and before the Course 2 Cycle 1 Day 1 dose, if applicable

l 9-17 days after last dose of avelumab

m +/- 10 days

n If imaging is used for response assessment

o Tests performed for End of Course 1 time point that were completed within 7 days prior to the Course 2 Cycle 1 Day 1 dose of avelumab do not need to be repeated for Course 2 Cycle 1 Day 1.

p within 90 days prior to subject enrollment

q Patients who experience a complete response or partial response will be evaluated every 6 weeks 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 patient status, dates of disease recurrence and interventions to treat recurrent disease. The first follow-up visit, 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) 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.

s As indicated in section 9.3, 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.
3.6 **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.

3.6.1 Criteria for removal from protocol therapy

Patients will be taken off treatment for the following:

- 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

3.6.2 Duration of Follow up

Patients who do not experience a complete response will be contacted 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 will be contacted annually for three years after completing the first 2 years’ worth of follow up clinic visits (for a total of approximately five years of follow up). The dates of disease recurrence and interventions to treat recurrent disease will be recorded.

3.6.3 Off-Study Criteria

Patients will be taken off study for the following:

- The patient voluntarily withdraws
- There is significant patient noncompliance
- The investigators decide it is in the patient’s best interest
- The patient completes follow-up
- Death

3.6.4 Off Protocol Therapy and Off-Study Procedure

Authorized staff must notify Central Registration Office (CRO) when a subject is taken off protocol therapy and when a subject is taken off-study. A Participant Status Updates Form from the web site (http://home.ccr.cancer.gov/Intra/eligibility/welcome.htm) main page must be completed and sent via encrypted email to: NCI Central Registration Office nxicentralregistration-l@mail.nih.gov.
3.7 STOPPING RULE

3.7.1 All protocol treatment will be temporarily stopped to allow for review of data and consultation with the FDA and IRB if either of the following events occur:

- Any treatment-related death
- Three ≥ Grade 3 Unexpected Serious Adverse Events

3.7.2 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 BIOSPECIMEN COLLECTION

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

4.1 CORRELATIVE STUDIES FOR RESEARCH

4.1.1 Biospecimen collection before the start of avelumab

- 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) will be collected prior to the first dose of avelumab. This is a total of 96 mL of blood. This blood will 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 avelumab. One CPT tube will be used to collect plasma which will be frozen in a 4mL vial. PBML from the remainder of the CPT tubes will be frozen in aliquots of 10 x 10^6 cells/vial. Send to Dr. Fran Hakim’s Pre-Clinical Core lab; Attention Jeremy Rose, Bldg. 10, room 12C216 contact phone: 301-594-5339.

- 16 mL of blood will be drawn to obtain serum for research purposes (2 SST tubes, 8 mL per tube) within 14 days prior to the first dose of avelumab. This will be processed in ETIB Pre-Clinical Core and frozen in aliquots of 0.5-1mL/vial. Send to Dr. Fran Hakim’s Pre-Clinical Core lab; Attention Jeremy Rose, Bldg. 10, room 12C216 contact phone: 301-594-5339.

- A research apheresis sample will be collected prior to first dose of avelumab. Apheresis collection will be 5 L volume (as close to 5 L as possible). Apheresis will only be performed on patients with adequate peripheral venous access. Cells will be transferred to Dr. Fran Hakim’s 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 avelumab. 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: Stacey Doran, MD 301-451-6957.

- 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 Dr. Fran Hakim’s Pre-Clinical Core lab. Assays will be performed retrospectively.

4.1.2 Biospecimen collection during treatment and follow-up

- Patients will return to the Clinical Center every two weeks for avelumab dosing. Blood and serum for research and TBNK testing will be obtained prior to each dose of avelumab. Blood for research will consist of:
  - 6 CPT tubes of Research Blood (48 mL) will be collected for immunological testing and processed as described in section 4.1.1. Attention Jeremy Rose, Bldg. 10, room 12C216 contact phone: 301-594-5339.
  - 1 SST tube (8 mL) of Research Blood will be obtained for serum collection and processed as described in section 4.1.1. Attention Jeremy Rose, Bldg. 10, room 12C216 contact phone: 301-594-5339.
- Papilloma and adjacent tissue samples will be collected by biopsy 2 weeks after the first dose of avelumab (9-17 days after the first dose). This should occur prior to second dose of avelumab. Repeat biopsies will be collected again two weeks after the third dose of avelumab (9-17 days after the third dose), which corresponds to the end of the first course (3 doses) of avelumab. These procedures should occur before Course 2, if applicable. Biopsies will again be collected at the time of completion debulking for patients who do not experience a complete tumor response. 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: Stacey Doran, MD 301-451-6957.
- A research apheresis sample will be collected 2 weeks after the first dose of avelumab (9-17 days after the first dose). This apheresis should occur before the second dose of avelumab. Apheresis will only be performed on patients with adequate peripheral venous access. Cells will be transferred to Dr. Fran Hakim's 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. If patients experience a 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 will be collected at these time points as described above.

4.1.3 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 will include all or some of the following: assessment of PD-L1 expression by papillomas and papilloma-infiltrating immune cells, testing of papillomas and normal appearing mucosa for HPV, 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 [25].

Generation and isolation of T cells

Papilloma-infiltrating T cells will be generated from papilloma biopsy specimens by culture of 2 mm tissue fragments in culture media with IL-2. Lymphocyte cultures will 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 will 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 will be autologous immature dendritic cells (DCs) generated from apheresis samples. The DCs will 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 [25].

HPV detection and genotyping

Testing will be performed by Dr. Hinrichs’ laboratory using PCR-based type-specific HPV detection and quantification assays [25].

Generation of papilloma cell lines.

When feasible, papilloma biopsy specimens will be sent to Richard Schlegel’s laboratory for the generation of papilloma cell lines for use in research at Georgetown University Medical Center. The specimens will be provided in a tube of sterile saline or similar sterile buffer. The specimens will be deidentified. The source of the specimens will be known to the NIH investigators but not the Georgetown University investigators.
Richard Schlegel  M.D., Ph.D.  
Professor and Oscar B. Hunter Chair  
Chair, Department of Pathology  
Director, Center for Cell Reprogramming  
Research Building, Room W500  
Georgetown University Medical School  
3900 Reservoir Road, NW  
Washington, DC 20057  
Telephone:  202-687-1655 

Transportation to Dr. Schlegel’s laboratory will be provided by courier. The courier will be Washington Express. The contact information for Washington Express is:

www.washingtonexpress.com 
800-939-5463

4.1.4 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.

4.1.5 Sample Storage, Tracking and Disposition

Preclinical Development and Clinical Monitoring Facility

- 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 the ETIB PDCMF’s Microsoft Excel databases on frozen cells and plasma. These databases are stored on the NCI group drive in the ETIB ‘PRECLINSERVICE’ folder. 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).

4.1.5.1 Hinrichs laboratory

- Samples may be transferred from Preclinical Development and Clinical Monitoring Facility to the Hinrichs laboratory for the research studies indicated in 4.1.3.

- 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.

4.1.6 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 report destroyed samples to the IRB if samples become unsalvageable because of environmental factors (ex. broken freezer or lack of dry ice in a shipping container) or if a patient withdraws consent. Samples will also be reported as lost if they are lost in transit between facilities or misplaced by a researcher. Freezer problems, lost samples or other problems associated with samples will also be reported to the IRB, the NCI Clinical Director, and the office of the CCR, NCI.
5 DATA COLLECTION AND EVALUATION

5.1 DATA COLLECTION

The PI will be responsible for overseeing entry of data into an in-house password protected 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 regulations 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, the IRB will be notified.

5.1.1 Concomitant medications recording:

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

5.1.2 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.

5.1.3 Collection of Adverse Events following surgery/procedure

Grade 1 or 2 adverse events that are clearly attributable to surgery/procedure will not be recorded or reported.

5.1.4 Collection of Adverse Events during Follow-up

Adverse Events that occur during the follow-up period will only be recorded if they are considered related to the avelumab.

5.2 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 [16]. 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) [26]. 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.

5.2.1 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.

5.2.2 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.

5.2.3 Definition of disease response
5.2.3.1 Complete Remission (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.

5.2.3.2 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

5.2.3.3 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.

5.2.3.4 Stable disease
- Not meeting criteria for CR, PR, or PD.

5.2.4 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)

<table>
<thead>
<tr>
<th>Target Lesions</th>
<th>Non-Target Lesions</th>
<th>New Lesions</th>
<th>Overall Response</th>
<th>Best Overall Response when Confirmation is Required*</th>
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<tbody>
<tr>
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<td>No</td>
<td>CR</td>
<td>≥4 wks. Confirmation**</td>
</tr>
<tr>
<td>CR</td>
<td>Non-CR/Non-PD</td>
<td>No</td>
<td>PR</td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>Not evaluated</td>
<td>No</td>
<td>PR</td>
<td>≥4 wks. Confirmation**</td>
</tr>
<tr>
<td>PR</td>
<td>Non-CR/Non-PD/not evaluated</td>
<td>No</td>
<td>PR</td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>Non-CR/Non-PD/not evaluated</td>
<td>No</td>
<td>SD</td>
<td>Documented at least once ≥4 wks. from baseline**</td>
</tr>
<tr>
<td>PD</td>
<td>Any</td>
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</tr>
<tr>
<td>Any</td>
<td>PD***</td>
<td>Yes or No</td>
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<tr>
<td>Any</td>
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<td>Yes</td>
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<td></td>
</tr>
</tbody>
</table>

* 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.
5.3 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 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40).

6 Safety Reporting Requirements/Data and Safety Monitoring Plan

6.1 Definitions

6.1.1 Adverse Event

An adverse event is defined as any reaction, side effect, or untoward event that occurs during the course of the clinical trial associated with the use of a drug in humans, whether or not the event is considered related to the treatment or clinically significant. For this study, AEs will include events reported by the patient, as well as clinically significant abnormal findings on physical examination or laboratory evaluation. A new illness, symptom, sign or clinically significant laboratory abnormality or worsening of a pre-existing condition or abnormality is considered an AE. All AEs must be recorded on the AE case report form.

All AEs, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed until return to baseline or stabilization of event. Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of at least possibly related to the agent/intervention should be recorded and reported as per sections 6.2, 6.3, 6.5.

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 Suspected adverse reaction

Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, ‘reasonable
possibility’ means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

6.1.3 Unexpected adverse reaction

An adverse event or suspected adverse reaction is considered “unexpected” if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application. "Unexpected” also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

6.1.4 Serious

An Unanticipated Problem or Protocol Deviation is serious if it meets the definition of a Serious Adverse Event or if it compromises the safety, welfare or rights of subjects or others.

6.1.5 Serious Adverse Event

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 drug experience
- 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.

6.1.6 Disability

A substantial disruption of a person’s ability to conduct normal life functions.

6.1.7 Life-threatening adverse drug experience

Any adverse event or suspected adverse reaction that places the patient or subject, in the view of the investigator or sponsor, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that had it occurred in a more severe form, might have caused death.

6.1.8 Protocol Deviation (NIH Definition)

Any change, divergence, or departure from the IRB-approved research protocol.
6.1.9 Non-compliance (NIH Definition)
The failure to comply with applicable NIH Human Research Protections Program (HRPP) policies, IRB requirements, or regulatory requirements for the protection of human research subjects.

6.1.10 Unanticipated Problem
Any incident, experience, or outcome that:

- Is unexpected in terms of nature, severity, or frequency in relation to
  (a) the research risks that are described in the IRB-approved research protocol and informed consent document; Investigator’s Brochure or other study documents, and
  (b) the characteristics of the subject population being studied; **AND**
- Is related or possibly related to participation in the research; **AND**
- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

6.2 NCI-IRB AND CLINICAL DIRECTOR REPORTING

6.2.1 NCI-IRB and NCI Clinical Director Expedited Reporting of Unanticipated Problems and Deaths
The Protocol PI will report in an NIH Problem form to the NCI-IRB and the NCI Clinical Director:

- All deaths, except deaths due to progressive disease
- All Protocol Deviations
- All Unanticipated Problems
- All non-compliance

Reports must be received within 7 days of PI awareness via iRIS.

6.2.2 NCI-IRB Requirements for PI Reporting at Continuing Review
The protocol PI will report to the NCI-IRB:

- A summary of all protocol deviations in a tabular format to include the date the deviation occurred, a brief description of the deviation and any corrective action.
- A summary of any instances of non-compliance
- A tabular summary of the following adverse events:
  - All Grade 2 unexpected events that are possibly, probably or definitely related to the research;
  - All Grade 3 and 4 events that are possibly, probably or definitely related to the research;
  - All Grade 5 events regardless of attribution;
All Serious Events regardless of attribution.

**NOTE**: Grade 1 events are not required to be reported.

6.2.3 NCI-IRB Reporting of IND Safety Reports

Only IND Safety Reports that meet the definition of an unanticipated problem will need to be reported to the NCI IRB.

6.3 **IND SPONSOR REPORTING CRITERIA**

An investigator must immediately report to the sponsor, using the mandatory MedWatch form 3500a, any serious adverse event, whether or not considered drug related, including those listed in the protocol or investigator brochure and must include an assessment of whether there is a reasonable possibility that the drug caused the event.

- All Grade 5 (fatal) events (except death due to progressive disease) must be reported via email within 24 hours. A complete report must be submitted within one business day.
- All other serious adverse events including deaths due to progressive disease must be reported within one business day

Study endpoints that are serious adverse events (e.g. all-cause mortality) must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the drug and the event (e.g. death from anaphylaxis). In that case, the investigator must immediately report the death to the sponsor.

Events will be submitted to the Center for Cancer Research (CCR) at: **CCRsafety@mail.nih.gov** and to the CCR PI and study coordinator.

6.3.1 Reporting Pregnancy

6.3.1.1 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. The potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agents (s) should be documented in box B5 of the MedWatch form “Describe Event or Problem”.

Pregnancy itself is not regarded as an SAE. However, as patients who become pregnant on study risk intrauterine exposure of the fetus to agents which may be teratogenic, the CCR is requesting that pregnancy should be reported in an expedited manner as **Grade 3 “Pregnancy, puerperium and perinatal conditions - Other (pregnancy)”** under the Pregnancy, puerperium and perinatal conditions SOC.

Congenital abnormalities or birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) should be followed up and documented.
If any pregnancy occurs in the course of the study, then the investigator should inform the Sponsor within 1 day, i.e., immediately, but no later than 24 hours of when he or she becomes aware of it.

The designated Sponsor representative will work with the investigator to ensure that all relevant information is provided to the Sponsor within 1 to 5 calendar days for SAEs and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

6.3.1.2 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 avelumab.

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 avelumab until 60 days after the last dose should, if possible, be followed up and documented.

6.4 REPORTING TO THE DIVISION OF ANTIVIRAL PRODUCTS (DAVP)

Any cases of myocarditis or other serious autoimmune AEs will be reported to the DAVP, even if such events are expected.

6.5 SAFETY REPORTING CRITERIA TO THE PHARMACEUTICAL COLLABORATORS:

All events listed below must be reported in the defined timelines to CCRsafety@mail.nih.gov.

The CCR Office of Regulatory Affairs will send all reports to the manufacturer as described below.

6.5.1 Serious and Unexpected Suspected Adverse Reaction (SUSAR)

Definition: A suspected adverse reaction to study treatment that is both serious and unexpected. The Investigator must report SUSARs within 24 hours of learning of the event to EMD Serono’s parent company, Merck via Fax: 781-681-2961 or email: gds@merckgroup.com.

6.5.2 Serious Adverse Event (SAE)

Definition: See Section 6.1.5. The Investigator must report SAEs within 24 hours of learning of the event to EMD Serono’s parent company, Merck via Fax: 781-681-2961 or email: gds@merckgroup.com.

6.5.3 Pregnancy

The Investigator 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.

6.5.4 Annual Report

The Investigator will provide a copy of the FDA Annual Report to EMD Serono/Merck at the time of submission to the FDA.
6.6 DATA AND SAFETY MONITORING PLAN

6.6.1 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. Adverse events will be reported as required above. Any safety concerns, new information that might affect either the ethical and or scientific conduct of the trial, or protocol deviations will be immediately reported to the IRB using iRIS and to the Sponsor.

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.

6.6.2 Sponsor Monitoring Plan

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 study endpoints; adherence to the protocol, regulations, 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 an NCI 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.

7 STATISTICAL CONSIDERATIONS

The trial will be conducted using a Simon optimal two-stage design; the objective is to rule out a 5% complete response rate ($p_0=0.05$) and target a 20% complete response rate ($p_1=0.20$).

The design will use $\alpha=0.10$ (10% chance of accepting a poor agent) and $\beta=.10$ (corresponding to 90% power--and 10% 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 37 evaluable patients have enrolled. If there are 1 to 3 complete responses in 37 patients, this would be considered unacceptably low, while if 4 or more patients have complete responses in 37 patients,
then the results will be considered sufficiently promising for further evaluation. Under the null hypothesis (5% complete response rate), the probability of early termination is 54.0%.

It is anticipated that up to 2 patients per month may enroll onto this trial; thus, up to 2 years may be required to complete accrual. The trial would require up to 37 total evaluable patients; the accrual ceiling will be set at 40 patients to allow for a small number of inevaluable patients.

8 COLLABORATIVE AGREEMENT

8.1 COOPERATIVE RESEARCH AND DEVELOPMENT AGREEMENT

- The study drug avelumab will be provided under a CRADA (EMD Serono, Inc – NCI CRADA# 02666/NCI MTA # 41332-16) between the manufacturer, EMD Serono, and the Center for Cancer Research, National Cancer Institute.

8.2 MATERIAL TRANSFER AGREEMENT

- An MTA is in place with Georgetown University Medical School (NCI MTA# 42132-17) for the samples discussed in section 4.1.3

9 HUMAN SUBJECTS PROTECTIONS

9.1 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.

9.2 PARTICIPATION OF CHILDREN

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

9.3 PARTICIPATION OF NIH SUBJECTS UNABLE TO GIVE CONSENT

Adults unable to give consent are excluded from enrolling in the protocol. However re-consent may be necessary and there is a possibility, though unlikely, that subjects could become decisionally impaired. For this reason and because there is a prospect of direct benefit from
research participation (section 9.5), all subjects will be offered the opportunity to fill in their wishes for research and care, and assign a substitute decision maker on the “NIH Advance Directive for Health Care and Medical Research Participation” form so that another person can make decisions about their medical care in the event that they become incapacitated or cognitively impaired during the course of the study. Note: The PI or AI will contact the NIH Ability to Consent Assessment Team for evaluation. For those subjects that become incapacitated and do not have pre-determined substitute decision maker, the procedures described in MEC Policy 87-4 for appointing a surrogate decision maker for adult subjects who are (a) decisionally impaired, and (b) who do not have a legal guardian or durable power of attorney, will be followed.

9.4 PARTICIPATION OF PREGNANT WOMEN

Based on its mechanism of action and data from animal studies, avelumab can cause fetal harm when administered to a pregnant woman. Human IgG1 is known to cross the placental barrier and avelumab is an immunoglobulin G1 (IgG1); therefore, avelumab 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 for at least 28 days prior, throughout the avelumab treatment and for at least 60 days after avelumab treatment.

9.5 EVALUATION OF BENEFITS AND RISKS/DISCOMFORTS

The experimental treatment has a chance to provide clinical benefit though this is unknown. The safety profile of avelumab has been established in treatment of over 700 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 avelumab and the biology or RRP that will help to advance treatment of RRP and other diseases.

9.5.1 Study drug risks

The risks associated with the study product are discussed in Section 10.1.4.

9.5.2 EUA and Biopsy Risks

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.
9.5.3 Risks associated with blood sampling

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

9.5.4 Risks associated with leukapheresis

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

9.5.5 Risks associated with CT scans

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. If a CT scan is used, there will also be a risk of exposure to radiation from up to 3 CT scans. The amount of radiation received in this study is 0.43 rem which is below the guideline of 5 rem (or 0.5 rem in children) per year allowed for research subjects by the NIH Radiation Safety Committee.

9.6 CONSENT AND ASSENT PROCESS AND DOCUMENTATION

The patient, along with family members or friends, will be presented with a detailed description of the protocol treatment. The specific requirements, objectives, and potential advantages and disadvantages will be presented. The Informed Consent document is given to the patient who is requested to review it and to ask questions prior to agreeing to participate in the treatment portion of this protocol. The patient will be reassured that participation on trial is entirely voluntary and that he/she can withdraw or decide against treatment at any time without adverse consequences. The research nurse, Principal Investigator or his designee is responsible for obtaining written informed consent from the patient.

If new safety information results in significant changes in the risk/benefit assessment, the consent form will be reviewed and updated as necessary. All subjects (including those already being treated) will be informed of the new information, be given a copy of the revised form, and asked to give their consent to continue in the study.

9.6.1 Telephone reconsent

Reconsent on this study may be obtained via telephone according to the following procedure: the informed consent document will be sent to the subject. An explanation of the change(s) in the study will be provided over the telephone after the subject has had the opportunity to read the consent form. The subject will sign and date the informed consent. A witness to the subject’s signature will sign and date the consent.

The original informed consent document will be sent back to the consenting investigator who will sign and date the consent form with the date the consent was obtained via telephone.

A fully executed copy will be returned via mail for the subject’s records. The informed consent process will be documented on a progress note by the consenting investigator and a copy of the informed consent document and note will be kept in the subject’s research record.

9.6.2 Enrollment of non-English speaking subjects

If there is an unexpected enrollment of a research participant for whom there is no translated extant IRB approved consent document, the principal investigator and/or those authorized to obtain informed consent will use the Short Form Oral Consent Process as described in MAS
Policy M77-2, OHSRP SOP 12, 45 CFR 46.117 (b) (2) and 21 CFR 50.27 (b) (2)). The summary that will be used is the English version of the extant IRB approved consent document. Signed copies of both the English version of the consent and the translated short form will be given to the subject or their legally authorized representative and the signed original will be filed in the medical record.

Unless the PI is fluent in the prospective subject’s language, an interpreter will be present to facilitate the conversation. Preferably someone who is independent of the subject (i.e., not a family member) will assist in presenting information and obtaining consent. Whenever possible, interpreters will be provided copies of the relevant consent documents well before the consent conversation with the subject (24 to 48 hours if possible).

We request prospective IRB approval of the use of the short form process for non-English speaking subjects and will notify the IRB at the time of continuing review of the frequency of the use of the Short Form.

10 PHARMACEUTICAL INFORMATION

10.1 AVELUMAB IND# 130884

Amino Acid Sequence: 4 polypeptide chains, which include 2 identical heavy chains with 440 amino acids and 2 identical light chains.

Other Names: MSB0010718C

Classification: Anti-PD-L1MAb

M.W.: 143,832 daltons

10.1.1 Mode of Action

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.

10.1.2 Description

Avelumab drug product is a sterile, clear, and colorless concentrate for solution intended for intravenous (i.v.) administration. The drug is presented at the concentrations of 10 mg/mL and 20 mg/mL in single-use glass vial containing 80 mg and 200 mg of avelumab, respectively.

10.1.3 Source

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

10.1.4 Toxicities

As of 01 June 2015, safety data of 717 subjects who were treated with 10 mg/kg of avelumab every 2 weeks and followed up for at least 4 weeks in the pooled tumor expansion cohort of Trial EMR 100070-001 were evaluated.
The most frequently observed treatment-related TEAEs (with an incidence of ≥ 2%) of any grade in the pooled expansion cohort were infusion-related reaction, fatigue, nausea, diarrhea, chills, and decreased appetite. Other frequently seen treatment-related TEAEs with an incidence < 5% but ≥ 2% included arthralgia, pyrexia, hypothyroidism, pruritus, vomiting, influenza-like illness, rash, anemia, AST increased, myalgia, asthenia, headache, ALT increased, dyspnea, and constipation.

Note: On this protocol, dry mouth has been observed with greater frequency than previously observed, from a CTCAE grade 1-2 intensity, and may be attributable to avelumab. This has been noted in the informed consent document.

10.1.5 Preparation

Avelumab 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 avelumab 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 avelumab 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.

10.1.6 Storage and Stability

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

10.1.7 Administration procedures

Avelumab is to be administered as an IV infusion, using a volumetric pump with a 0.2/0.22 micron in-line filter at the protocol-specified dose. It is not to be administered as an IV push or bolus injection. At the end of the infusion, flush the line with a sufficient quantity of normal saline.

10.1.8 Potential Drug Interactions

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


## APPENDICES

### 12.1 Appendix A: Performance Status Criteria

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal activity. Fully active, able to carry on all pre-disease performance without restriction.</td>
</tr>
<tr>
<td>1</td>
<td>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).</td>
</tr>
<tr>
<td>2</td>
<td>In bed &lt;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.</td>
</tr>
<tr>
<td>3</td>
<td>In bed &gt;50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.</td>
</tr>
<tr>
<td>4</td>
<td>100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.</td>
</tr>
<tr>
<td>5</td>
<td>Dead.</td>
</tr>
</tbody>
</table>

### 12.2 **APPENDIX B: VOICE HANDICAP INDEX-10**

<table>
<thead>
<tr>
<th></th>
<th>Never (0)</th>
<th>Almost never (1)</th>
<th>Sometimes (2)</th>
<th>Almost always (3)</th>
<th>Always (4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>My voice makes it difficult for people to hear me</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>People have difficulty understanding me in a noisy room</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>People as “what’s wrong with your voice?”</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I feel as though I have to strain to produce voice</td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>My voice difficulties restrict personal and social life</td>
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<td></td>
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<tr>
<td>The clarity of my voice is unpredictable</td>
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<td></td>
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<tr>
<td>I feel left out of conversations because of my voice</td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>My voice problem causes me to lose income</td>
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<td></td>
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<td></td>
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<tr>
<td>My voice problem upsets me</td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>My voice makes me feel handicapped</td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

**Total Score:**

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As published in:


12.3 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

12.3.1 Gastrointestinal irAEs

<table>
<thead>
<tr>
<th>Severity of Diarrhea / Colitis (NCI-CTCAE v4.03)</th>
<th>Management</th>
<th>Follow-up</th>
</tr>
</thead>
</table>
| **Grade 1**
Diarrhea: < 4 stools/day over Baseline
Colitis: asymptomatic | Continue avelumab 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 avelumab therapy
Symptomatic treatment | If improves to Grade 1:
Resume avelumab 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 avelumab 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 avelumab 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 |
### 12.3.2 Dermatological AEs

<table>
<thead>
<tr>
<th>Grade of Rash (NCI-CTCAE v4)</th>
<th>Management</th>
<th>Follow-up</th>
</tr>
</thead>
</table>
| **Grade 1 to 2**                                      | Symptomatic therapy (for example, antihistamines, topical steroids)  
Continue avelumab therapy                                                                                                                   | If persists > 1 to 2 weeks or recurs:  
Consider skin biopsy  
Delay avelumab 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 avelumab therapy  
If worsens:  
Treat as Grade 3 to 4 |
| Covering ≤ 30% body surface area                     |                                                                                                                                                                                                            |                                                                                                                                                                                                          |
| **Grade 3 to 4**                                      | Delay or discontinue avelumab 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 avelumab therapy                                                                                                                     |
| Covering > 30% body surface area; life threatening consequences |                                                                                                                                                                                                            |                                                                                                                                                                                                          |
### 12.3.3 Pulmonary AEs

<table>
<thead>
<tr>
<th>Grade of Pneumonitis (NCI-CTCAE v4)</th>
<th>Management</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Grade 1</strong>&lt;br&gt; Radiographic changes only</td>
<td>Consider delay of avelumab therapy&lt;br&gt;Monitor for symptoms every 2 to 3 days&lt;br&gt;Consider Pulmonary and Infectious Disease consults</td>
<td>Re-image at least every 3 weeks&lt;br&gt;If worsens: Treat as Grade 2 or Grade 3 to 4</td>
</tr>
<tr>
<td><strong>Grade 2</strong>&lt;br&gt; Mild to moderate new symptoms</td>
<td>Delay avelumab therapy&lt;br&gt;Pulmonary and Infectious Disease consults&lt;br&gt;Monitor symptoms daily, consider hospitalization 1.0 mg/kg/day methylprednisolone IV or oral equivalent&lt;br&gt;Consider bronchoscopy, lung biopsy</td>
<td>Re-image every 1 to 3 days&lt;br&gt;If improves:&lt;br&gt;When symptoms return to near Baseline, taper steroids over at least 1 month and then resume avelumab therapy and consider prophylactic antibiotics&lt;br&gt;If not improving after 2 weeks or worsening: Treat as Grade 3 to 4</td>
</tr>
<tr>
<td><strong>Grade 3 to 4</strong>&lt;br&gt; Severe new symptoms; New / worsening hypoxia; life-threatening</td>
<td>Discontinue avelumab therapy&lt;br&gt;Hospitalize&lt;br&gt;Pulmonary and Infectious Disease consults&lt;br&gt;2 to 4 mg/kg/day methylprednisolone IV or IV equivalent&lt;br&gt;Add prophylactic antibiotics for opportunistic infections&lt;br&gt;Consider bronchoscopy, lung biopsy</td>
<td>If improves to Baseline:&lt;br&gt;Taper steroids over at least 6 weeks&lt;br&gt;If not improving after 48 hours or worsening:&lt;br&gt;Add additional immunosuppression (for example, infliximab, cyclophosphamide, IV immunoglobulin, or mycophenolate mofetil)</td>
</tr>
</tbody>
</table>
### 12.3.4 Hepatic AEs

<table>
<thead>
<tr>
<th>Grade of Liver Test Elevation (NCI-CTCAE v4)</th>
<th>Management</th>
<th>Follow-up</th>
</tr>
</thead>
</table>
| **Grade 1**  
Grade 1 AST or ALT > ULN to 3.0 x ULN and / or total bilirubin > ULN to 1.5 x ULN  
| Continue avelumab 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 avelumab therapy  
| Increase frequency of monitoring to every 3 days  
| If returns to Baseline:  
| Resume routine monitoring, resume avelumab 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 avelumab therapy |
| **Grade 3 to 4**  
AST or ALT > 5 x ULN and / or total bilirubin > 3 x ULN  
| Discontinue avelumab 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 |
### Cardiac AEs

<table>
<thead>
<tr>
<th>Cardiac irAEs</th>
<th>Management</th>
<th>Follow-up</th>
</tr>
</thead>
</table>
| **Myocarditis**       | Withhold avelumab 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 avelumab 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 avelumab.  
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](https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines)  
AHA guidelines website: [http://professional.heart.org/professional/GuidelinesStatements/searchresults.jsp?q=&y=&t=1001](http://professional.heart.org/professional/GuidelinesStatements/searchresults.jsp?q=&y=&t=1001)
## 12.3.6 Endocrine AEs

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

STAGING ASSESSMENT FOR RECURRENT LARYNGEAL PAPILLOMATOSIS

PATIENT INITIALS:________________ DATE OF SURGERY:__________ SURGEON:________________ 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___(?)

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 5.2