INTRODUCTION

We invite you to take part in a research study at the National Institutes of Health (NIH).

First, we want you to know that:

Taking part in NIH research is entirely voluntary.

You may choose not to take part, or you may withdraw from the study at any time. In either case, you will not lose any benefits to which you are otherwise entitled. However, to receive care at the NIH, you must be taking part in a study or be under evaluation for study participation.

You may receive no benefit from taking part. The research may give us knowledge that may help people in the future.

Second, some people have personal, religious or ethical beliefs that may limit the kinds of medical or research treatments they would want to receive (such as blood transfusions). If you have such beliefs, please discuss them with your NIH doctors or research team before you agree to the study.

Now we will describe this research study. Before you decide to take part, please take as much time as you need to ask any questions and discuss this study with anyone at NIH, or with family, friends or your personal physician or other health professional.

Why is this study being done?

The main purpose of this study is to see if Avelumab works in treating recurrent respiratory papillomatosis (RRP). Another goal of this study is to look at the safety of the study drug. Avelumab is designed to block the activity of a certain protein in the body, PD-L1, which has been associated with allowing abnormal or infected cells to avoid detection and elimination by the immune system.
Avelumab is an investigational drug, which means that the Food and Drug Administration (FDA) has not approved it for sale or for marketing for recurrent respiratory papillomatosis. This study is a Phase 2 clinical trial. Phase 2 trials test the effectiveness (if the drug works) and safety of an investigational drug.

Avelumab belongs to a family of molecules called anti-PD-L1 antibodies. PD-L1 is a protein on the surface of cells that regulates whether that cell can be killed by immune system cells. PD-L1 is thought to be able to stop or decrease the response of the immune system to different kinds of diseased cells, such as cancer cells or cells infected with a virus. Avelumab interferes with the activity of PD-L1 and is thought to have an effect on the immune system (in particular white blood cells) that may cause an immune response or increase the effectiveness of the response.

Avelumab has been tested at different dose levels to see which dose is safe and well tolerated when given once every two weeks. Based on this information it was determined that 10mg/kg drug strength would be used in this research trial.

Additional purposes of the trial are to study the side effects of avelumab and to find out whether avelumab can reduce papillomas. Another goal of the study is to learn more about your disease and your response to this investigational drug. To do this, we will draw blood and collect tissue to measure certain “biomarkers”. “Biomarkers” refer to different types of markers found in the blood and tissue that are associated with the disease and/or your response to the investigational drug. For this, samples of your blood and papilloma will be collected. The purpose of this research is to find out if there are any disease-related markers which may help in predicting how subjects respond to avelumab. This is described in more detail below.

**Why are you being asked to take part in this study?**

You are being asked to take part in this trial because you have aggressive recurrent respiratory papillomatosis and your disease may not have responded adequately to available treatments.

**How many people will take part in this study?**

Up to 40 patients will be enrolled on this trial.

**Description of Research Study**

**What will happen if you take part in this research study?**

**Before you begin the study**

Before receiving the investigational drug, you will have several tests performed to check whether the trial is suitable for you. Your doctor will review your medical history and the drugs that you are currently taking as well as the previous treatments of your disease to determine whether you can participate in this trial. A small part of tumor tissue that was previously collected from you, will be used to confirm the diagnosis of recurrent respiratory papillomatosis. Some of these tests or procedures are part of regular care and may be done even if you are not being considered to join the study. If you have had some of these tests or procedures recently, they may or may not
have to be repeated. The following tests and procedures will be performed prior to starting treatment:

1. Complete history and physical examination, including height, weight and vital signs (temperature, blood pressure, heart rate, breathing rate).

2. Blood tests (about 1 tablespoon) to check your blood counts, blood chemistries and viral studies.

3. For females of child-bearing potential, a pregnancy test will be done. You will not be able to participate if you are pregnant.

4. An endoscopy procedure in the clinic called flexible nasopharyngolaryngoscopy. For this procedure, the doctor uses a flexible endoscope (a small tube with a built-in camera) to look at the structures inside the nose, throat, larynx (voice box) and upper windpipe. This is a procedure to assess your throat and larynx; you will likely have already had this procedure before.

**During the study**

**Before Treatment**

If you are determined eligible to be in the study, you will have the following additional tests that will be performed for research purposes only:

1. Endoscopy procedure under anesthesia (sedation or general anesthesia). This procedure allows us to make sure we know where all of your papilloma disease is located, to make sure that your airway will be open enough to undergo the experimental treatments and to get biopsies of your papilloma. If we are concerned that your papilloma may cause breathing issues while you receive the experimental treatment, we may remove some of the papilloma to make your breathing safer. This pre-treatment biopsy is required because it will confirm the diagnosis and provide information that is critical to the goals of this study.

The biopsy will be studied in the research laboratory to evaluate additional proteins and characteristics in your papilloma. You will not receive results of the research testing because they are being conducted in a research lab and are not valid for treatment purposes. The research testing on the biopsy may include growing cell lines (cells which keep dividing and growing in the laboratory, sometimes for years allowing us to continually study those cells).

In addition, a portion of the biopsy will be reviewed by the pathologist at your study site to confirm your diagnosis of benign papilloma. You will receive the results of this review.

2. You will have blood collected (approx. 2 tablespoons) for research testing. You will not receive results of the research testing.

3. Voice Handicap Index-10 assessment questionnaire.

4. CT scan of chest (if necessary) to evaluate any papillomas in your lungs.
5. You will have an apheresis procedure for research. The apheresis procedure involves inserting a catheter (tube) into your vein to allow your blood to be collected. White blood cells will be separated from the rest of your blood and stored until the time they are used for research and the rest of the blood will be returned to you through the same catheter it came out of or through second needle in your other arm. We will try to use IV catheters already in place, but may need to give you an additional IV catheter. You will be asked to sign a separate consent for this procedure.

After the research samples have been collected, you will begin treatment. Your participation in the Study Treatment Period may continue for as long as you are receiving benefit and you do not meet any of the withdrawal criteria.

Avelumab will be administered at a dose of 10 mg/kg every other week (Day 1 of a 14-day cycle (weeks 1, 3, 5, 7, 9 and 11) for up to 12 weeks total (6 cycles). Avelumab will be given as an infusion through a vein (IV) over a 60-minute period.

You will be monitored closely while you are participating in this trial. Some medications may interact with avelumab and should be avoided. You will need to inform your study doctor about any prescription and non-prescription medications you are taking. Your doctor will help determine whether you should continue these drugs, whether you need to change the way you are taking these drugs, or whether you need to switch to another medication.

Some of the tests done before starting treatment will be repeated 6 and 12 weeks after starting treatment to check on how the treatment is working.

**Every 2 weeks while receiving study treatment:**
- Physical examination which may include flexible nasopharyngolaryngoscopy in the clinic.
- Vital signs and weight.
- Pregnancy test in women of childbearing potential.
- Blood tests (about 1 tablespoon) to check your blood counts, blood chemistries and other tests to monitor your health.
- Blood collection (approx. 3-4 tablespoons) for research testing.
- Review of side effects that you have experienced and medications that you are taking.
- Voice Handicap Index-10 assessment questionnaire.
- Infusion of avelumab.

**Additional studies at a single time point two weeks after the initial dose**
- Endoscopy procedure under anesthesia (sedation or general anesthesia) to see if there are clinical signs of inflammation in your airway or if there is blockage of your airway and to
obtain biopsies which will be used for research purposes to evaluate how your disease is responding to the treatment.

- Apheresis procedure to collect white blood cells (also called leukocytes) which will be used for research.

**Every 6 weeks while receiving study treatment (performed at 6 and 12 weeks after start of treatment):**

- Physical examination.
- Flexible nasopharyngolaryngoscopy in the clinic.
- Voice Handicap Index-10 assessment questionnaire.
- CT scan of chest (if used for response assessment) to evaluate your RRP status.

**When you are finished taking the study treatment:**

- Endoscopy procedure under anesthesia (sedation or general anesthesia) to either perform a biopsy to verify that your papilloma is gone if you had a complete response to the treatment, or to remove all visible papilloma with normal surgery techniques if you do not have a complete response to the treatment.
- If you respond to the treatment, you will be evaluated every 6 weeks (3 times), then every 12 weeks (3 times), then every 26 weeks (two times) or until you experience disease progression.
- You will be evaluated 30 days after the last dose of avelumab.
- If you do not experience a response to treatment you will be contacted annually to document additional disease recurrence and treatments that you have received.
- Evaluations will include:
  - Physical Exam
  - Pregnancy test in women of childbearing potential
  - Vital signs.
  - Flexible nasopharyngolaryngoscopy in the clinic.
  - Blood tests (about 1 tablespoon) to check your blood counts, blood chemistries and other tests to monitor your health.
  - Blood collection (approx. 3-4 tablespoons) for research testing.
  - Review of side effects that you have experienced and medications that you are taking.
  - Voice Handicap Index-10 assessment questionnaire.
Birth Control

If you are a woman who is breast feeding or pregnant, you may not take part in the study because we don’t know how this medicine would affect your baby or your unborn child. If you are a woman who can become pregnant, or are the partner of a woman who can become pregnant, you will need to practice two effective forms of birth control (one highly effective method and one other effective method) for at least 28 days prior, throughout the avelumab treatment and for at least 60 days after avelumab treatment. If you think that you or your partner is pregnant, you should tell your study doctor or nurse at once.

Highly Effective Methods

- Intrauterine device (IUD)
- Hormonal (birth control pills, injections, implants) Tubal ligation
- Partner’s vasectomy

Other Effective Methods

- Latex condom
- Diaphragm
- Cervical Cap

Risks or Discomforts of Participation

What side effects or risks can I expect from being in this study?

What could be the side effects of the study drug?

In a clinical study like this one, every risk or side effect cannot be predicted. Each person’s reaction to a study drug, device or procedure may be different. You may have a side effect or be at risk for symptoms, illnesses and/or complications that could not be predicted by your study doctor or the sponsor of this clinical study. If such side effects occur, you must inform your study doctor immediately.

The following side effects (regardless of relationship to study drug) have been observed in more than 10% of the 1300 patients treated with the study drug. Some of the side effects can be serious.

Common side effects:

- Fatigue
• Nausea, vomiting
• During or after drug infusion having:
  o change in blood pressure
  o fever
  o chills
  o difficulty breathing which might be serious
• Diarrhea
• Constipation
• Decreased appetite
• Weight loss
• Abdominal pain
• Anemia (decrease of red blood cells)
• Cough
• Shortness of breath
• Fever
• Chills (feeling cold)

Less common side effects:
• Inflammation in the lungs (pneumonitis that can be fatal)
• Inflammation of the colon (colitis) which can lead to abdominal pain and diarrhea with or without blood. If left untreated, this may lead to a tear in the wall of the intestine which can be serious and life threatening.
• Inflammation of the liver called hepatitis, that can cause liver failure and death
• Inflammation of the thyroid (thyroiditis)
• Feeling faint, joint and abdominal pain, salt craving, skin darkening like a suntan
• Weight gain
• Anxious, angry
• Can’t sleep
• Increased sweating
• Hair loss
• Muscle pain, tenderness and/or weakness
• Inflammation of the heart (myocarditis) (May cause your heart to have difficulty pumping blood throughout your body, which can cause chest pain, difficulty breathing, swelling in your legs. You may also experience a fast or irregular heartbeat that can cause dizziness or fainting. Sometimes this condition can lead to death.)
• Skin changes (rash, itchiness, redness)
• Allergic reactions, causing:
  o swelling of the face, lips and throat
  o breathing difficulties which might be serious
The side effects listed above may or may not be caused by problems with your lungs, colon, liver, thyroid, adrenal gland, muscles, heart, and skin. They may be temporary, long term, permanent or result in death. However, most of these side effects are reversible. That means they will stop once the drug is discontinued.

Other immune-related events were observed with similar drugs in this class, such as type I diabetes mellitus, pituitary dysfunction, inflammation of the kidney, inflammation of the eyes, inflammation of the joint, inflammation of the brain, inflammation of the pancreas and inflammation of the nervous system.

Allergic reactions or reactions in the context with the infusions might occur during treatment. Infusion related reactions have been observed under treatment with the study drug, as seen for other similar drugs. In general, these reactions are mild to moderate and can be handled with appropriate drugs, but in rare cases, life-threatening and even fatal reactions might occur, which require advanced cardiac life support.

For the prevention of infusion-related adverse effects and possible allergic reactions you will receive a premedication of an antihistamine drug and paracetamol (acetaminophen) before every infusion.

There is a chance the study drug could lead to Tumor Lysis Syndrome (TLS) due to tumor shrinkage. TLS is when cancer cells break down and the body has to get rid of the broken-up cell parts. Sometimes your body can’t remove the cell parts quickly enough and the levels of some products in your blood, such as salts and acids, can rise. This can happen especially in participants with large tumors or a high number of white cells in the blood. TLS can lead to serious problems, such as effects on your kidney and heart (including abnormal heart rhythms) or seizures. These side effects can result in needing kidney dialysis (a special machine to remove toxins from the blood) or be fatal. Your study doctor knows to watch out for signs of this condition and how to treat this condition should it occur.

Any side effects or other health issues occurring during the study will be followed up by the study doctor.
Other side effects linked to medical procedures during the trial

Blood samples
Each time a blood sample is needed, a needle will be put into a vein in your arm (or into your central venous catheter, if you have one). You may feel pain when the needle goes through the skin. Other side effects associated with drawing your blood for blood tests may include infection, bruising, redness, discomfort or bleeding at the site of the needle stick, and possible lightheadedness and fainting.

Electrocardiogram (ECG)
An electrocardiogram or ECG is a test that records the electrical activity of the heart. It is used to measure the rate and regularity of heartbeats as well as the size and position of the heart chambers, and the presence of any damage to the heart. For this test, you will be asked to lie down, and small patches that have an adhesive edge with a gel in the middle, called electrodes, will be placed on your arms, legs, and chest. The areas where the electrodes are placed will be cleaned and, if needed, some hair may be shaved or clipped to allow for better attachment of the electrodes. The adhesive from the patches may irritate your skin.

CT scan
During a CT scan, you're briefly exposed to much more radiation than you would be during a plain X-ray. Radiation exposure potentially increases your risk of developing cancer. Although rare, the intravenous (IV) contrast material involved in some CT scans causes medical problems or allergic reactions in some people. Most reactions are mild and result in hives or itchiness. In rare instances, an allergic reaction can be serious and potentially life threatening. Make sure to tell your study doctor if you've ever had a prior reaction to contrast material during medical tests.

Papilloma biopsy under anesthesia
You are required to have general anesthesia three times for this protocol – before treatment starts, two weeks after treatment has started, and after completing treatment. Although rare, serious risks associated with general anesthesia include an adverse drug reaction, stroke, heart attack or death. You will be asked to sign a separate consent prior to each procedure involving anesthesia. Aside from the risk of anesthesia, this procedure carries a risk of post-operative tongue or throat discomfort that may last for several days and a very small risk of a chipped tooth from the instruments in your mouth. We use special tooth guards to prevent this from happening.

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

Apheresis
The most common side effects from this procedure are pain and bruising at the catheter site. You may also experience tingling of the lips and fingers due to the medicine used to keep blood
from clotting. You may feel faint or light-headed during or after the procedure. Rarely this procedure may cause bleeding or infection at the catheter site.

Other
It is possible that other side-effects could occur which are not described in this consent form. It is also possible that you could have a side effect that has not occurred before.

Potential Benefits of Participation
Are there benefits to taking part in this study?
The aim of this study is to see if this experimental treatment will cause your papilloma to shrink. We do not know if you will receive personal, medical benefit from taking part in this study. These potential benefits could include shrinking of your papilloma or lessening of your papilloma-associated symptoms. Because there is not much information about the drug’s effect on your disease, we do not know if you will benefit from taking part in this study, although the knowledge gained from this study may help others in the future who have papilloma and other types of growths caused by viruses or cancers.

Alternative Approaches or Treatments
What other choices do I have if I do not take part in this study?
Instead of being in this study, you have these options:
- Getting treatment or care for your papilloma without being in a study
- Taking part in another study
Please talk to your doctor about these and other options.

Research Subject’s Rights
What are the costs of taking part in this study?
If you choose to take part in the study, the following will apply, in keeping with the NIH policy:

- You will receive study treatment at no charge to you. This may include surgery, medicines, laboratory testing, x-rays or scans done at the Clinical Center, National Institutes of Health (NIH), or arranged for you by the research team to be done outside the Clinical Center, NIH if the study related treatment is not available at the NIH.
- There are limited funds available to cover the cost of some tests and procedures performed outside the Clinical Center, NIH. You may have to pay for these costs if they are not covered by your insurance company.
• Medicines that are not part of the study treatment will not be provided or paid for by the Clinical Center, NIH.

• Once you have completed taking part in the study, medical care will no longer be provided by the Clinical Center, NIH.

Will your medical information be kept private?
We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

• The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), which are involved in keeping research safe for people.

• National Cancer Institute Institutional Review Board

• Qualified representatives from EMD Serono, the pharmaceutical company who produces avelumab.

A description of this clinical trial will be available on [http://www.Clinicaltrials.gov](http://www.Clinicaltrials.gov), as required by U.S. Law. This Web site will not include information that can identify you. At most the Web site will include a summary of the results. You can search this Web site at any time.

Stopping Therapy
Your doctor may decide to stop your therapy for the following reasons:

• if he/she believes that it is in your best interest
• if your papilloma progresses while you are receiving treatment
• if you have side effects from the treatment that your doctor thinks are too severe
• if new information shows that another treatment would be better for you
• if the sponsor, the FDA, the Institutional Review Board or your doctor decides to stop or interrupt the study
• If you cannot or do not come to your clinic visits or do not follow the study procedures

In this case, you will be informed of the reason therapy is being stopped.

You can stop taking part in the study at any time. However, if you decide to stop taking part in the study, we would like you to talk to the study doctor and your regular doctor first.

If you decide at any time to withdraw your consent to participate in the trial, we will not collect any additional medical information about you. However, according to FDA guidelines, information collected on you up to that point may still be provided to EMD Serono or designated...
representatives. If you withdraw your consent and leave the trial, any samples of yours that have been obtained for the study and stored at the NCI can be destroyed upon request. However, any samples and data generated from the samples that have already been distributed to other researchers or placed in the research databases cannot be recalled and destroyed.

**Conflict of Interest**

The National Institutes of Health (NIH) reviews NIH staff researchers at least yearly for conflicts of interest. This process is detailed in a Protocol Review Guide. You may ask your research team for a copy of the Protocol Review Guide or for more information. Members of the research team who do not work for NIH are expected to follow these guidelines but they do not need to report their personal finances to the NIH.

Members of the research team working on this study may have up to $15,000 of stock in the companies that make products used in this study. This is allowed under federal rules and is not a conflict of interest.

The National Institutes of Health and the research team for this study are using a drug, developed by EMD Serono through a joint study with your researchers and the company. The company also provides financial support for this study.

**Use of Specimens and Data for Future Research**

To advance science, it is helpful for researchers to share information they get from studying human samples. They do this by putting it into one or more scientific databases, where it is stored along with information from other studies. A researcher who wants to study the information must apply to the database and be approved. Researchers use specimens and data stored in scientific databases to advance science and learn about health and disease.

We plan to keep some of your specimens and data that we collect, use them for future research and share them with other researchers. We will not contact you to ask about each of these future uses. These specimens and data will be stripped of identifiers such as name, address or account number, so that they may be used for future research on any topic and shared broadly for research purposes. Your specimens and data will be used for research purposes only and will not benefit you. It is also possible that the stored specimens and data may never be used. Results of research done on your specimens and data will not be available to you or your doctor. It might help people who have cancer and other diseases in the future.

If you do not want your stored specimens and data used for future research, please contact us in writing and let us know that you do not want us to use your specimens and/or data. Then any specimens that have not already been used or shared will be destroyed and your data will not be used for future research. However, it may not be possible to withdraw or delete materials or data once they have been shared with other researchers.
OTHER PERTINENT INFORMATION

1. Confidentiality. When results of an NIH research study are reported in medical journals or at scientific meetings, the people who take part are not named and identified. In most cases, the NIH will not release any information about your research involvement without your written permission. However, if you sign a release of information form, for example, for an insurance company, the NIH will give the insurance company information from your medical record. This information might affect (either favorably or unfavorably) the willingness of the insurance company to sell you insurance.

The Federal Privacy Act protects the confidentiality of your NIH medical records. However, you should know that the Act allows release of some information from your medical record without your permission, for example, if it is required by the Food and Drug Administration (FDA), members of Congress, law enforcement officials, or authorized hospital accreditation organizations.

2. Policy Regarding Research-Related Injuries. The Clinical Center will provide short-term medical care for any injury resulting from your participation in research here. In general, no long-term medical care or financial compensation for research-related injuries will be provided by the National Institutes of Health, the Clinical Center, or the Federal Government. However, you have the right to pursue legal remedy if you believe that your injury justifies such action.

3. Payments. The amount of payment to research volunteers is guided by the National Institutes of Health policies. In general, patients are not paid for taking part in research studies at the National Institutes of Health. Reimbursement of travel and subsistence will be offered consistent with NIH guidelines.

4. Problems or Questions. If you have any problems or questions about this study, or about your rights as a research participant, or about any research-related injury, contact the Principal Investigator, Christian S. Hinrichs, M.D., Building 10, Room 4B04, Telephone: 240-760-6059. You may also call the Clinical Center Patient Representative at 301-496-2626. If you have any questions about the use of your specimens or data for future research studies, you may also contact the Office of the Clinical Director, Telephone: 240-760-6070.

5. Consent Document. Please keep a copy of this document in case you want to read it again.
<table>
<thead>
<tr>
<th>COMPLETE APPROPRIATE ITEM(S) BELOW:</th>
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<tbody>
<tr>
<td><strong>A. Adult Patient’s Consent</strong></td>
</tr>
<tr>
<td>I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby consent to take part in this study.</td>
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Signature of Adult Patient/ Legal Representative
Date

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<th><strong>B. Parent’s Permission for Minor Patient.</strong></th>
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<tr>
<td>I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby give permission for my child to take part in this study.</td>
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</table>

(Attach NIH 2514-2, Minor’s Assent, if applicable.)

Signature of Parent(s)/ Guardian
Date

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<th><strong>C. Child’s Verbal Assent (If Applicable)</strong></th>
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<tr>
<td>The information in the above consent was described to my child and my child agrees to participate in the study.</td>
</tr>
</tbody>
</table>

Signature of Parent(s)/ Guardian
Date
Print Name

**THIS CONSENT DOCUMENT HAS BEEN APPROVED FOR USE FROM JUNE 26, 2017 THROUGH JUNE 25, 2018.**

Signature of Investigator
Date

Signature of Witness
Date

Print Name

**PATIENT IDENTIFICATION**

**CONSENT TO PARTICIPATE IN A CLINICAL RESEARCH STUDY (Continuation Sheet)**
- Adult Patient or
- Parent, for Minor Patient

NIH-2514-1 (07-09)
P.A.: 09-25-0099
File in Section 4: Protocol Consent