INVESTIGATOR: Charalampos Floudas, MD, DMSc, MS

STUDY TITLE: Phase II Trial of Immunotherapeutic HPV vaccine PRGN-2009 with Pembrolizumab before Standard Treatment in Subjects with Newly Diagnosed HPV-Associated Oropharyngeal Cancer

STUDY SITE: NIH Clinical Center

Cohort: *Affected patient*

Consent Version: *05/06/2024*

WHO DO YOU CONTACT ABOUT THIS STUDY?

Principal Investigator: Charalampos Floudas, MD, DMSc, MS

[redacted]

KEY INFORMATION ABOUT THIS RESEARCH

This consent form describes a research study and is designed to help you decide if you would like to be a part of the research study.

You are being asked to take part in a research study at the National Institutes of Health (NIH). This section provides the information we believe is most helpful and important to you in making your decision about participating in this study. Additional information that may help you decide can be found in other sections of the document. Taking part in research at the NIH is your choice.

You are being asked to take part in this study because you have been newly diagnosed with stage I (T1,2 N1)/II/III HPV-positive oropharyngeal squamous cell carcinoma (OPSCC).

The purpose of this study is to determine if an HPV vaccine given with immunotherapy can improve the immune response to prevent your tumor from coming back in the future.

The study drugs you may receive are called immunotherapy and include:

- Pembrolizumab is a drug that blocks a pathway that prevents your immune system from fighting your cancer.
- HPV vaccine (PRGN-2009) is a type of vaccine which is designed to teach your immune system how to target and kill cancer cells.
- When these drugs work together, they may have a better effect on eliciting an immune response against your cancer than when they work alone.

The use of PRGN-2009 and pembrolizumab in this study is considered investigational, which means that this combination has not been approved by the U.S. Food and Drug Administration (FDA) to treat OPSCC. However, the FDA has given us permission to use the combination of HPV vaccine and pembrolizumab in this study.

Pembrolizumab is already FDA-approved for use in other types of cancers. For your type of cancer it is approved for metastatic cancer, but for your stage it is considered experimental.

If you decide to join this study, here are some of the most important things that you should know that will happen:

- We will first do some basic tests to make sure you qualify for the trial. These include: standard blood tests and scans to test your health, including your heart and viral infections, and see the status of your disease
- If you fit the study requirements and decide to take part, you will receive the study drugs in the outpatient clinic as follows:
    - PRGN-2009 will be given by injection under the skin on Week 1 and Week 3, for a total of 2 doses.
    - Pembrolizumab will be given by intravenous (IV) infusion (a small catheter is inserted into a vein allowing the solution to be given) only once with the first vaccine dose. The infusion will take about 30 minutes.
- During the study you will be seen each time you receive the vaccine and once after the second vaccination. Each visit will take about 5-6 hours.
- You will have clinical, laboratory, and imaging tests to see how you are doing and to see if your disease is responding to the treatment. We will also collect research samples from you, including tumor tissue, blood, and saliva.
- About four weeks after your study therapy has ended, you may be seen in the clinic and possibly have more clinical and research tests. These visits are important for your safety and if you cannot come in person, you will be contacted by phone for follow-up.
- We will contact you by phone for long term follow-up at about 3 and 6 months after starting the study and then once a year until 5 years to ask about your condition and survival.
- You may experience side effects from taking part in this study. Some can be mild or very serious, temporary, long-lasting, or permanent, and may include death. Examples of some of the side effects include tiredness, nausea, infection, anemia (low red blood cells), fever, rash, diarrhea. You may also have side effects from some of the procedures (such as the biopsy). All of the possible side effects are described in more detail later in the consent form.
- If you are capable of becoming pregnant, you must agree to use birth control during the study and for 4 months after the last dose of pembrolizumab or 2 months after the last dose of PRGN-2009. You must also stop breastfeeding.

You may not benefit from taking part in this study. However, this study and the results from our research may help others in the future.

You are free to stop participating in the trial at any time. If you decide to stop, the study doctor may ask you to agree to certain tests to make sure it is safe for you to stop.

The remaining document will now describe the research study in more detail. This information should be considered before you make your choice. Members of the study team will talk with you

about the information in this document. Some people have personal, religious, or ethical beliefs that may limit the kinds of medical or research interventions in which they would want to participate. Take the time you need to ask any questions and discuss this study with NIH staff, and with your family, friends, and personal health care providers.

IT IS YOUR CHOICE TO TAKE PART IN THE STUDY

You may choose not to take part in this study for any reason. If you join this study, you may change your mind and stop participating in the study at any time and for any reason. In either case, you will not lose any benefits to which you are otherwise entitled. However, to be seen at the NIH, you must be taking part in a study or are being considered for a study. If you do choose to leave the study, please inform your study team to ensure a safe withdrawal from the research.

WHY IS THIS STUDY BEING DONE?

The purpose of this research study is to determine if an HPV vaccine (PRGN-2009) given with immunotherapy (pembrolizumab) can increase your immune response to help your body fight the cancer and perhaps to help prevent your tumor from coming back in the future after other treatment.

We are asking you to join this research study because you have been newly diagnosed with stage I (T1,2 N1)/II/III HPV-positive OPSCC.

The use of PRGN-2009 and pembrolizumab in this study is considered investigational, which means that this combination has not been approved by the U.S. Food and Drug Administration (FDA) to treat newly-diagnosed non-metastatic OPSCC. However, the FDA has given us permission to use the combination of PRGN-2009 and pembrolizumab in this study.

WHAT WILL HAPPEN DURING THE STUDY?

Below is a description of what will be asked of you and what will occur if you decide to take part in this study.

Before you begin the study – Screening

Before beginning the study, you will need to undergo tests and/or procedures to help your doctor verify whether you can participate. This is called screening. Most of the exams, tests, and procedures you will have are part of the usual approach for your disease. However, there are some extra procedures that you will need to have if you take part in this study. If you have already undergone some of these examinations very recently, your doctor may decide not to repeat them. Briefly, these tests include:

- Confirmation of diagnosis: we will review your pathology records to confirm your OPSCC diagnosis. If your pathology reports are not available, we will collect tissue (biopsy) from you to confirm your diagnosis.
- Medical history: to review any past or current medical conditions.
- Physical examination: including height, weight, vital signs
- Performance status: a review of your symptoms and your ability to perform your normal activities.

- Immunology evaluation if you have shown prior allergic reactions to pembrolizumab or other immunotherapy drugs.
- Routine blood tests (about 2 tablespoons):
    - to check your blood counts, blood minerals, liver and kidney function
    - to measure how well your blood clots
    - to check for hepatitis B and C
    - to check for HIV: As part of this study, we will test you for infection with human immunodeficiency virus (HIV), the virus that causes acquired immunodeficiency syndrome (AIDS). If you are infected with HIV, you may still be able to take part in this study. We will tell you what the results mean, how to find care, how to avoid infecting others, how we report HIV infections, and the importance of informing your partners at possible risk because of your HIV infection.
- Pregnancy test: If you are a person who can have children, a urine or serum pregnancy test will be done. The results of the blood test must be negative for you be allowed in the study.
- Computer tomography (CT) and fluorodeoxyglucose-positron emission tomography (^{18}FDG-PET)/CT scan to image your neck and chest.

If the tests show that you are not able to take part in the study, you will not be able to continue. Your study doctor will discuss other care options with you.

During the study – Treatment

Once it is decided that you are eligible to participate in this study, you will begin study treatment.

During your participation you will receive the HPV vaccine (PRGN-2009) in combination with pembrolizumab. You will receive the HPV vaccine by injection under the skin twice, on Day 1 and Day 15. Pembrolizumab will be given by an intravenous infusion only once, just after and on the same day as the first vaccine dose.

Before you start taking any new medicines, including medicines, vitamins and herbal supplements that you can buy 'over-the-counter', please talk to the study doctor to make sure they are allowed on this study.

While you are taking study medications, we will perform some tests and examinations for safety and to test the effect of the study therapy. We will also collect samples from you for purposes of research only. You will need to be seen in clinic at the NIH Clinical Center before you start your treatment, each time you receive the HPV vaccine and once after, up to 2 weeks after your second vaccine dose.

The assessments and tests to be done include:

- Physical exams and measures of your vital signs, and any current symptoms of your condition.
- Review of your medications (prescription, supplement, and over the counter).
- Performance status to see how you function in your daily activities

- Standard blood tests (about up to 2 ½ teaspoon per visit and no more than 8 teaspoons in an 8 week period) to measure your organ function, such as liver and kidney, thyroid, white and red blood cells, platelets, blood electrolytes and others
- Standard urine test
- Urine or blood pregnancy test in people who are able to have children
- Electrocardiogram (EKG) to measure your heart function (for research, at baseline, completion visit, and safety follow-up only).
- Imaging with CT and PET scans (MRI, if needed) before you start the treatment (neck and chest) and up to 2 weeks after your second vaccine dose (CT scan to the neck only at your completion visit). The study team will use these scans to see if the treatment is helping your cancer.

Additional research testing

In addition to the tests that we will conduct to determine whether you are having side effects or if you are responding to the study therapy, we will also collect samples from you for purposes of research only. Research testing will be done on your blood, saliva, and tumor tissue to help us determine the effects of the study drugs on your body and how your immune system is responding to therapy.

The following samples will be collected for research purposes only:

The samples included for these studies include:

- Blood samples (up to 9 tablespoons/visit and no more than 43 tablespoons in an 8 week period): some of these research tests include measuring the levels of blood chemicals, called cytokines, how your immune cells respond to study treatment, and to measure the levels of the virus that causes your cancer. Research blood will be drawn before starting treatment, each time you receive the HPV vaccine, and up to 2 weeks after your second vaccine dose.
- Saliva samples (about 1 ½ tablespoons): collected before starting treatment, each time you receive the HPV vaccine, and up to 2 weeks after your second vaccine dose to measure levels of viruses that may cause your cancer.
- Tissue biopsies: collected before you start treatment and up to 2 weeks after your second vaccine dose. You may be asked to sign a separate consent document at the time of each procedure per routine clinical practice. Tumor biopsies will be done by an ENT specialist using an ultrasound machine to guide the biopsy needle into the tumor to ensure accuracy. Biopsies may be performed under local anesthesia (numbing medicine) or general anesthesia.

All of your samples collected for research purposes on this study (such as the tumor and normal tissue) may be used to look for specific changes in the DNA in tumors that could be used to develop new ways of diagnosing and treating cancer. DNA (also called deoxyribonucleic acid) in the cells carries genetic information and passes it from one generation of cells to the next – like an instruction manual. Normal tissue contains the DNA (instructions) that you were born with, DNA

in tumor cells has changed – or mutated – and we think that change in the DNA is what causes tumors to form and to grow.

To look at the DNA of your tumor and determine which parts of the DNA have mutated, we will use what is called "whole exome sequencing." This where we will do special tests in the lab to look at the entire protein-coding sequence, or order, of how the DNA in your tumor is put together.

To examine the tumor and normal tissue we may use several different techniques depending on the type of tissue we collect. These could include growing cell lines (cells which keep dividing and growing in the laboratory, sometimes for years allowing us to continually study those cells) and looking in detail at the parts of the genes that produce specific proteins.

However, you should know that the analyses that we perform in our laboratory are for research purposes only; they are not nearly as accurate as the tests that are performed in a laboratory that is certified to perform genetic testing or testing for routine clinical care. For these reasons, we will not give you the results of the research tests done on your research samples in most cases. There may be exceptions to what we share with you and this is described later in this consent form in the section for "Return of research results".

When you are finished taking the drugs (treatment)

Completion Visit
After you complete the treatment, you will be asked to return to the NIH Clinical Center within 7 days after you have had last dose of study drug.

At this visit, you will be asked questions about your health, get a physical exam, and undergo similar blood, heart monitoring, and imaging as during treatment.

If you are unable to return to the NIH Clinical Center for this visit, we may contact you or your local physician to collect clinical data and ask for your symptoms.

Safety Visit
We will ask you to come to the clinic for a safety check-up, about 28 days after the last dose of the vaccine to see how you are doing.

At this visit, you will be asked questions about your health, get a physical exam, and undergo similar blood, heart monitoring and imaging tests as during treatment.

If you are unable to travel to the NIH Clinical Center, you can complete the required evaluations with your local medical provider and you will be contacted by phone by the study doctor.

Follow-up

You will be contacted by phone about 3 and 6 months after starting the study and about once a year for 5 years after completing the study to check on your disease status and to see how you are feeling. If we are unable to contact you, we will contact your next of kin.

HOW LONG WILL THE STUDY TAKE?

If you agree to take part in this study, your involvement is expected to last for 5 years after completion of your surgery or chemoradiotherapy.

You will be seen a few times during treatment. The outpatient visits usually take about 2-3 hours but should not take longer than 8 hours.

HOW MANY PEOPLE WILL PARTICIPATE IN THIS STUDY?

Approximately 20 people will receive study therapy at the NIH.

WHAT ARE THE RISKS AND DISCOMFORTS OF BEING IN THE STUDY?

If you choose to take part in this study, you are at risk for side effects. The study doctors do not know who will or will not have side effects. Some side effects may go away soon, some may last a long time, and some may never go away. It is also possible that you may experience more than one side effect at the same time. Some side effects may be mild. Other side effects may be very serious and even result in death. You will be watched carefully for any side effects. You should talk to your study doctor about any side effects that you have while taking part in the study.

Risks of the Study Treatment

PRGN-2009

- Injection site reaction (e.g., redness, swelling)
- Fever
- Flu like symptoms (e.g., fatigue, headache, muscle aches)
- Poor appetite
- Increase in blood sugar
- Skin rash

In addition, there is a risk of having delays in standard therapy (e.g., surgery or radiation) which may result in a reduced chance of being cured from cancer.

If any of these side effects occur, you must inform your study doctor immediately.

Pembrolizumab

VERY COMMON, SOME MAY BE SERIOUS In 100 people receiving pembrolizumab, more than 20 and up to 100 may have:
• Itching of the skin • Loose or watery stools • Cough

COMMON, SOME MAY BE SERIOUS In 100 people receiving pembrolizumab, from 5 to 20 may have:
• Joint pain • Rash • Fever • Back pain • Pain in your belly

COMMON, SOME MAY BE SERIOUS In 100 people receiving pembrolizumab, from 5 to 20 may have:
• Loss of skin color • Not enough thyroid hormone, so you may feel tired, gain weight, feel cold, or have infrequent or hard stools (hypothyroidism) • Low levels of salt in the blood that may cause you to feel tired, feel confused, have a headache, have muscle cramps, and/or feel sick to your stomach (hyponatremia)

UNCOMMON, SOME MAY BE SERIOUS In 100 people receiving pembrolizumab, from 1 to 5 may have:
• Inflammation of the lungs, so you may feel short of breath and cough (pneumonitis) • Too much thyroid hormone, so you may feel anxious, feel angry, have trouble sleeping, feel weak, tremble, sweat, feel tired, and/or have loose and watery stools (hyperthyroidism) • Infusion reaction, where you may feel dizzy or faint, feel flushed, get a rash, have a fever, feel short of breath, experience a decrease in your blood pressure at the time of receiving your infusion (IV) or just after, or have pain at the site of infusion • Inflammation of the bowels/gut, which may cause severe pain in your belly with loose or watery stools, and black, tarry, sticky stools or stools with blood or mucus (colitis) • Inflammation of the skin, so you may have peeling of the skin, itchiness, and/or skin redness. The skin inflammation (i.e., peeling, itching, and redness) could also be widespread throughout your body. More severe skin reactions may involve the inside of your mouth, the surface of your eye and genital areas, and/or may cause the top layer of your skin to peel from all over your body, which can cause severe infection. (Severe skin reactions, including Stevens-Johnson syndrome or toxic epidermal necrolysis)

RARE, SOME MAY BE SERIOUS In 100 people receiving pembrolizumab, less than 1 person may have:
• Inflammation of the nerves that may cause pain, weakness, or tingling in your hands and feet, and may spread to your legs, arms, and upper body leading to severe muscle weakness and possible temporary paralysis (Guillain-Barré syndrome) • Inflammation of the muscles so you may feel weak or have pain in your muscles (myositis) • Inflammation of the pancreas (a gland in your abdomen that controls sugar levels), so you may have severe pain in the top part of your belly that may move to your back, feel sick to your stomach, and have vomiting that gets worse when you eat (pancreatitis)

RARE, SOME MAY BE SERIOUS

In 100 people receiving pembrolizumab, less than 1 person may have:

- Inflammation of the eye, so you may have eye redness, blurred vision, sensitivity to light, eye pain, see floaters, or have headaches (uveitis)
- Inflammation of the liver that may make you feel sick to your stomach and vomit, feel like not eating, feel tired, have a mild fever, a pain in the right side of your belly, yellow eyes and skin, and dark urine (hepatitis)
- Inflammation of the pituitary gland (a gland in the head), which may cause you to feel sick to your stomach or have headaches, changes in your behavior, double vision, few to no menstrual cycles, weakness, vomiting and dizziness, or fainting (hypophysitis)
- Adrenal glands (glands on top of the kidneys) that may not make enough hormone, which could cause tiredness, weight loss, muscle weakness, feeling faint, having joint, muscle, and belly aches, nausea, vomiting, loose or watery stools, fever, salt craving, and sometimes darkening of the skin like a suntan (adrenal insufficiency)
- Type 1 Diabetes, a condition that can cause too much sugar in your blood, feeling thirstier than usual, frequent urination, and weight loss. You are likely to need regular insulin shots.
- Inflammation of the kidney, so you may pass less urine or have cloudy or bloody urine, swelling, and low back pain (nephritis)
- Inflammation of the middle layer of your heart wall that may cause your heart to have difficulty pumping blood throughout your body, which can cause chest pain, shortness of breath, and swelling of the legs. You may experience a fast or irregular heartbeat that may cause dizziness or fainting. (myocarditis)
- Inflammation of the thyroid gland, an organ that makes and stores thyroid hormones. This condition may lead to a change in your heart rate, blood pressure, body temperature, and the rate at which food is converted into energy. (thyroiditis)
- A condition that may make you feel weak and tired and might have drooping of the eyelids, blurred or double vision, difficulty swallowing, slurred speech, weakness in your arms and legs, or difficulty breathing (myasthenic syndrome/myasthenia gravis including exacerbation)
- The formation of small clusters of immune cells (called granulomas) in parts of your body such as your lymph nodes, eyes, skin, or lungs (sarcoidosis)
- Inflammation of the brain with confusion and fever. This may also include: disorientation, memory problems, seizures (fits), changes in personality and behavior, difficulty speaking, weakness or loss of movement in some parts of your body, and loss of consciousness (encephalitis)
- Inflammation of the spinal cord with pain, numbness, tingling, or weakness in the arms or legs, bladder or bowel problems including needing to urinate more frequently, urinary incontinence, difficulty urinating, and constipation (myelitis)
- Inflammation of the blood vessels (vasculitis). Symptoms will depend on the particular blood vessels that are involved in the inflammatory process, for example; if it is your

RARE, SOME MAY BE SERIOUS In 100 people receiving pembrolizumab, less than 1 person may have:
skin, you may get a rash. If your nerves are not getting enough blood, you could have numbness and weakness. You may also experience fever, weight loss, and fatigue • If you need a tissue transplant, including a transplant of the tissue in your eye, this may be rejected by your immune system, which can destroy the transplanted tissue.

Additionally, since pembrolizumab was approved in September 2014, the following side effects have been reported by people receiving pembrolizumab. These side effects were voluntarily reported from a group of people of unknown size. It is not possible to estimate the frequency of this side effect:

- Inflammation of the joints which may include joint pain, stiffness and/or swelling (arthritis)
- Severe responses of the immune system that cause the body to attack its own blood cells, spleen, liver, lymph nodes, skin, and brain. This may include fever, rash, inflammation of the liver, yellowing of the skin, an enlarged liver and spleen, low blood counts, and enlarged lymph nodes. The nervous system may also be affected and cause confusion, seizures and even coma. (hemophagocytic lymphohistiocytosis)
- Change in eyesight, eye pain, whitish patches on the skin and hearing loss (Vogt-Koyanagi-Harada syndrome
- Inflammation and scarring of the bile ducts (tubes that carry digestive fluid that is made in the liver). This can cause symptoms similar to those seen with inflammation of the liver (hepatitis) such as pain in right side of your belly, yellow eyes and skin, feeling tired, and itching (sclerosing cholangitis).

Risks of Study Procedures

- **Blood samples:** Side effects of blood draw include pain and bruising in the area where the needle was placed, lightheadedness, and rarely, fainting and infection. When large amounts of blood are collected, a low red blood cell count (anemia) can develop. We will not collect more than 9 tablespoons of blood any day of the study or 43 tablespoons within 8 weeks.
- **Electrocardiogram (EKG):** Some skin irritation can occur where the ECG (also referred to as EKG) electrodes are placed. Once the electrodes are placed, the test will begin, is completely painless, and generally takes less than a minute to perform. After the test, the electrodes are removed.
- **CT and PET scans:** You may receive a contrast agent injected into your arm as part of your scan. Contrast agents can cause allergic reactions and kidney damage. Allergic reactions can include mild itching associated with hives but can also result in a serious life-threatening emergency from difficulty breathing. If this occurs, it is treatable. You may feel discomfort when the contrast material is injected. You may feel warm, flushed, get a metallic taste in your mouth or, rarely, may make you vomit or feel sick to your stomach. Please ask the study doctor if you have questions about the risks of these scans.

- **MRI:** Magnetic resonance imaging (MRI) uses a strong magnetic field and radio waves to take pictures of the body. We will obtain pictures of your chest, abdomen and pelvis for this study. The MRI scanner is a metal cylinder surrounded by a strong magnetic field. People are at risk for injury from the MRI magnet if they have some kinds of metal in their body. It may be unsafe for you to have an MRI scan if you have pacemakers or other implanted electrical devices, brain stimulators, some types of dental implants, aneurysm clips (metal clips on the wall of a large artery), metal prostheses (including metal pins and rods, heart valves, and cochlear implants), permanent eyeliner, tattoos, an implanted delivery pump, or shrapnel fragments. Welders and metal workers may have small metal fragments in the eye. You will be screened for these conditions before having any MRI scan. If you have a question about metal in your body, you should inform the staff. You will be asked to complete an MRI screening form before each MRI scan you have.

  In addition, all magnetic objects (like watches, coins, jewelry, and credit cards) must be removed before entering the MRI scan room.

  People with fear of confined spaces may become anxious during an MRI. Those with back problems may have back pain or discomfort from lying in the scanner. The noise from the scanner is loud enough to damage hearing, especially in people who already have hearing loss. Everyone having a research MRI scan will be fitted with hearing protection. If the hearing protection comes loose during the scan, you should let us know right away.

  There are no known long-term risks of MRI scans.

- **Gadolinium:** During part of the MRI you will receive gadolinium, a contrast agent, through an intravenous (IV) catheter (small tube). It will be done for both research and medical purposes.

  It is not known if MRI with contrast is completely safe for a developing fetus. Therefore, all women of childbearing potential will have a pregnancy test performed no more than 24 hours before each MRI scan with contrast. The scan will not be done if the pregnancy test is positive.

  The risks of an IV catheter include bleeding, infection, or inflammation of the skin and vein with pain and swelling.

  Mild symptoms from gadolinium infusion occur in fewer than 1% of those who receive it and usually go away quickly. Mild symptoms may include coldness in the arm during the injection, a metallic taste, headache, and nausea. In an extremely small number, fewer than one in 300,000 people, more severe symptoms have been reported including shortness of breath, wheezing, hives, and lowering of blood pressure. You should not receive gadolinium if you previously had an allergic reaction to it. You will be asked about such allergic reactions before gadolinium is given.

  People with kidney disease are at risk for a serious reaction to gadolinium contrast called "nephrogenic systemic fibrosis (NSF)". This condition always involves the skin and can also involve the muscles, joints and internal organs. NSF has resulted in a very small

number of deaths. A blood test of your kidney function may be done within the month before an MRI scan with gadolinium contrast. You will not receive gadolinium for a research MRI scan if your kidney function is below the safe level.

Most of the gadolinium contrast leaves the body in the urine. However, the FDA has issued a safety alert that indicates small amounts of gadolinium may remain in the body for months to years. The effects of the retained gadolinium are not clear. At this time, retained gadolinium has not been linked to health risks in people whose kidneys work well. Some types of gadolinium contrast drugs are less likely to remain in the body than others. In this study, we will use the gadolinium contrast drugs that are less likely to remain in the body.

- **Urine and saliva collection:** There are no physical risks associated with these collections.
- **Tissue biopsy:** The biopsies will be done with a procedure called **endoscopy and nasopharyngo-laryngoscopy**. In this procedure, a physician gently places a small, thin, flexible endoscope with a camera down through your nose to view your upper airway anatomy above the vocal cords. This procedure takes only a few minutes, is painless and is performed under local anesthesia. It is a normal part of an ENT exam. Risks of clinic endoscopy include bleeding from nose or sudden drop in heart rate if body reacts to certain triggers, each of which occur in <1% of all patients. If your tumors are not accessible in the clinic or a biopsy in the clinic is deemed unsafe by the study doctor, biopsies may be performed in the operating room under general anesthesia. Risks of operative biopsies include post-op bleeding (<1% of all patients), dental damage from laryngoscopy instrumentation (<1% of all patients) and temporary tongue abnormal sensation (<10% of all patients) that resolves within a few days.
- **Local anesthesia**: Tissue biopsies may be done under local anesthesia. Potential side effects of local anesthesia include drowsiness, headaches, blurred vision, twitching muscles or shivering, continuing numbness, weakness or pins and needles sensation.
- **General anesthesia**: Tissue biopsies may be done under general anesthesia. Side effects of general anesthesia may include temporary confusion, difficulty passing urine, bruising or soreness from the IV drip, nausea and vomiting, shivering and feeling cold, and sore throat.

Other Study Risks

Side effects of this investigational treatment may cause delay in scheduled curative therapy, which may result in a reduced chance of being cured from cancer.

What are the risks related to pregnancy?

For people who could possibly become pregnant

The effect of PRGN-2009 and pembrolizumab on the risk of birth defects, miscarriage, or other bad outcomes when taken during pregnancy or while breastfeeding is unknown. To reduce the risk of any harmful effects, people who are pregnant, trying to become pregnant, or breastfeeding are not allowed to participate in studies using PRGN-2009 and pembrolizumab.

If you are a person who could possibly become pregnant (you have not completed menopause, had a hysterectomy and/or both tubes and/or both ovaries removed) and you have a partner who is able to father children, a blood/urine pregnancy test will be performed, and it must be negative to continue in the study. In women 40 years old and older, blood pregnancy tests may sometimes give a false positive or "indeterminate" result and additional testing may be required to confirm your eligibility for the study. You will also have additional blood/urine tests at some study visits, as described above, and they also must be negative for you to continue in the study.

You and your partner must agree to either abstain completely from vaginal intercourse for the duration of the study and for 4 months after the last dose of pembrolizumab or 2 months after the last dose of PRGN-2009, or use a highly effective method of contraception for the same length of time. Highly effective methods include (a) partner vasectomy, (b) bilateral tubal ligation, (c) intrauterine devices (IUDs), (d) hormonal implants (such as Implanon), or (e) other hormonal methods (birth control pills, injections, patches, vaginal rings). If you and your partner are not currently using one of these methods your study doctor will discuss options with you, given your medical condition, your personal preferences, and the level of effectiveness required for this study. Because no birth control method is 100% effective, you should notify your study doctor immediately if you think there is any chance you could be pregnant, even if you have had a recent negative pregnancy test.

If you do become pregnant during the study, your study doctor will stop the study drug, withdraw you from the study, and notify the sponsor. You will be followed for the duration of the pregnancy to better understand the potential effects of the study drug on pregnancy outcomes.

For men who are able to father children

It is unknown whether pregnancies that began while the father was taking PRGN-2009 and pembrolizumab are at increased risk for birth defects, miscarriages, or other bad outcomes. To reduce the risk of any harmful effects, men who are trying to become fathers are not allowed to participate in this study.

If you are able to father children and your partner could possibly become pregnant (she has not completed menopause, or has not had a hysterectomy and/or both tubes and/or both ovaries removed), you and your partner must agree to either abstain completely from vaginal intercourse for the duration of the study and for 4 months after the last dose of pembrolizumab or 2 months after the last dose of PRGN-2009 after your last dose of study drug, or use a highly effective method of contraception for the same length of time. Highly effective methods include (a) vasectomy, (b) bilateral tubal ligation, (c) intrauterine devices (IUDs), (d) hormonal implants (such as Implanon), or (e) other hormonal methods (birth control pills, injections, patches, vaginal rings). If you and your partner are not currently using one of these methods your study doctor will discuss options with you, given your medical condition, your personal preferences, and the level of effectiveness required for this study.

You should not donate sperm for the duration of the study and for 4 months after the last dose of pembrolizumab or 2 months after the last dose of PRGN-2009.

You should notify your partner about your participation in this study, and the potential risks to pregnancies that begin while you are taking the study drug. If your partner does become pregnant during the study, you should notify your study doctor, and your partner should notify their doctor.

Your partner will be asked for permission to collect information about the pregnancy to better understand the potential effects of the study drug on pregnancy outcomes.

What are the risks of radiation from being in the study?

During your participation in this research study, you will be exposed to radiation from 3 neck CT scans, 2 chest CT scans, and 2 PET/CT. The amount of radiation exposure from these procedures is equal to approximately 3.23 rem. A rem is a unit of absorbed radiation. This amount of radiation is greater than the NIH Radiation Guidelines of 0.5 rem per year for participants less than 18 years old.

Every day, people are exposed to low levels of radiation that come from the sun and the environment around them. The average person in the United States receives a radiation exposure of 0.3 rem per year from these sources. This type of radiation is called "background radiation." No one knows for sure whether exposure to these low amounts of radiation is harmful to your body.

The CT and PET/CT scans that you get in this study will expose you to the roughly the same amount of radiation as 10.8 years' worth of background radiation. Most of the time, this amount of extra radiation is not harmful to you. However, scientists believe that being exposed to too much radiation can cause harmful side effects. This could include getting a new cancer. We estimate that this could happen in about 1 out of every 1000 people who get a very large amount of extra radiation.

WHAT ARE THE BENEFITS OF BEING IN THE STUDY?

You might not benefit from being in this study. However, you could benefit from being in this study if the medications help your immune system attack your tumor, which could reduce the size of the tumor and reduce your symptoms or improve your chances of survival.

Are there any potential benefits to others that might result from the study?

There is a need for new treatments in patients with HPV associated cancers as standard therapies often do not work. In the future, other people might benefit from this study because of the knowledge gained from the outcome of this trial using a novel immunotherapy.

WHAT OTHER OPTIONS ARE THERE FOR YOU?

Before you decide whether or not to be in this study, we will discuss other options that are available to you. Instead of being in this study, you could choose to take part in a different study, if one is available. You could choose to be treated with surgery, radiation or with drugs already approved by the FDA for your disease without participating in a trial.

DISCUSSION OF FINDINGS

New information about the study

If we find out any new information that may affect your choice to participate in this study, we will get in touch with you to explain what we have learned. This may be information we have learned while doing this study here at the NIH or information we have learned from other scientists doing similar research in other places.

Return of research results

The results of the standard tests, including any genetic tests, performed in certified labs and facilities during the research will be available to you as part of your medical record.

The results of any research procedures will not be returned to you with the exception of secondary genetic findings as discussed below.

In this study, we will use a test that looks at all or most of your genes or DNA. This test may find gene changes that are not related to what is being studied in this research. These are called "secondary findings". Most of the time when we look for these, we do not find anything. If we were to look for them in 100 people, we would expect them in only about 2 to 4 of those people.

If we discover a secondary finding that might be important to you or your family's health, we plan to tell you about this. However, before we can tell you, we may need to do the test again in another laboratory to be sure that the result is correct. To do so, we may need to ask you to submit another sample for testing. Once these results are available, we will invite you to schedule a visit, in person (at our expense) or remote so that you we can give you more information about this result and to help you seek follow-up care outside of the NIH if it is needed. If you are unable to see us, we will provide a referral to a local genetic healthcare provider (at your expense). The NIH will not generally provide any further follow-up testing or care for this condition for you or your family.

We may not be testing the samples we have collected from you for several years. Because of this, just because you have not heard from us, you should not assume that you do not have any gene changes that might be important for your health.

We also do not know all the gene changes that cause can cause health problems. We could learn later that some gene changes that now we do not think cause health problems are of concern. We will look for gene changes only once and will look for those that are known to cause problems at the time we are looking. We do not plan to look again at a later time for new secondary findings.

It is up to you if you want us to tell you about any secondary findings. At any point you can tell us that you do not want to us to contact you or tell you about any secondary findings.

We can only provide these results to you. If you want us to tell anyone else, then you must provide us with a signed written release of medical information request.

It is very important for you to keep us updated on how to contact you. If we do not have up to date information, we will not be able to get in touch with you to collect an additional sample or tell you about a secondary finding. If your contact information changes, providing us with the new information is your responsibility. If you no longer actively being seen by the study team or at our study site, please contact the Principal Investigator or other researcher(s) (see the first page or "Problems or Questions" section later in this document) to tell us of your new contact information.

If you have questions or concerns about learning this kind of genetic information, please speak with someone from the study team.

Risks of returning secondary genetic findings

- The evaluation for unexpected gene changes is limited and may not be as complete as clinical genetic testing that might be available to you outside of the research study.

- If an unexpected gene change result is confirmed, then that test result will go into your NIH medical record. These documents are confidential, but other NIH investigators can see them.
- Learning about the changes in your genes could mean something about your family members and might cause you or your family distress. Before joining the study, it may be helpful to talk with your family members about whether they want you to share your results with them.
- If a gene change is found, it may reveal whether a particular parent passed on the change to a biological child.
- You may receive a result for an unexpected gene change that turns out not to cause that health condition. This may cause you unnecessary distress or lead to unnecessary medical testing risks and costs.

Benefits of returning secondary genetic findings

An unexpected gene change result may be useful because you may be able to do something about it to protect your health or to help you plan for your future.

Protections against misuse of genetic information

This study involves genetic testing on samples. Some genetic information can help predict future health problems of you and your family and this information might be of interest to your employers or insurers. The Genetic Information Nondiscrimination Act (GINA) is a federal law that prohibits plans and health insurers from requesting genetic information or using genetic information. It also prohibits employment discrimination based on your health information. However, GINA does not address discrimination by companies that sell life insurance, disability insurance, or long-term care insurance. GINA also does not protect you against discrimination based on an already-diagnosed condition or disease that has a genetic component.

EARLY WITHDRAWAL FROM THE STUDY

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 disease worsens or comes back during treatment
- if you have side effects from the treatment that your doctor thinks are too severe
- if you become pregnant
- if the PRGN-2009 and/or pembrolizumab may become unavailable
- if new information shows that another treatment would be better for you
- if you do not follow the study rules
- if the study is stopped for any reason

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

After therapy is stopped we would like to see you for a safety visit 28 days after your last dose.

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 [redacted]., or designated representatives.

STORAGE, SHARING AND FUTURE RESEARCH USING YOUR SPECIMENS AND DATA

Will your specimens or data be saved by the study team for use in other studies?

As part of this study, we are obtaining specimens and data from you. We plan to store and use these specimens and data for studies other than the one described in this consent form that are going on right now, as well as studies that may be conducted in the future. The specimens and data will be kept in a way that we will still know that they came from you (i.e., they will be identifiable to us). If we use your identifiable specimens or data for future research, our study will be reviewed and approved by an Institutional Review Board who will make sure that we are protecting your confidentiality. These future studies might help us better understand HPV-positive OPSCC or other diseases or conditions. This could include studies to develop other research tests, treatments, drugs, or devices, that may lead to the development of a commercial product by the NIH and/or its research or commercial partners. There are no plans to provide financial compensation to you if this happens. Also, it is unlikely that we will learn anything from these studies that may directly benefit you.

I give permission for my identifiable specimens and data to be stored and used by the study team for future studies as described above.

_____ Yes _____ No

Initial Initial

Will your specimens or data be shared with other researchers for use in other studies?

We may share your specimens and data with other researchers. The other researchers may be doing studies in similar areas to this study or in other unrelated areas. These researchers may be at NIH, other research centers and institutions, or at commercial entities.

One way that we may share your data is by putting it into a large database called a repository, which is a way to make it widely available to the research community. If we do place your data in a repository, it will be labeled with a code, (not with your name or other information that could be used to easily identify you). Even though it will only be labeled with a code, some types of data, in particular data about your genes (called genetic or genomic data), can be used to figure out who you are, although this is difficult to do, and we think it is unlikely to happen.

The data in the repository will only be available to qualified researchers. These researchers must receive permission before they are allowed to access the data. Before receiving the data, the researchers must promise that they will not try to figure out the identity of the research participants.

If we do share your specimens or data, we will know that the specimens and data came from you. However, the other researchers will not know that they came from you (i.e., they will be de-identified).

I give permission for my **de-identified** specimens and data to be shared with and used by other researchers for future studies.

_____ Yes _____ No

Initial Initial

In some cases, it may help other researchers to know that the specimens or data were collected from you (i.e., they will have your identifiers). If we share your identity with other researchers, their study will be reviewed and approved by an Institutional Review Board who will make sure that the study team is protecting your confidentiality.

I give permission for my **identifiable** specimens and data to be shared with and used by other researchers for future studies.

_____ Yes _____ No

Initial Initial

Information about all the people (including you) in this study may be combined to create what is called summary information. The summary information may be placed in a database and will be made available to researchers only if they are granted permission. However, the summary information may still be shared in scientific publications without permissions. This information will help the researchers understand if some patterns are more common than others among everyone who was a part of this study. The risk of anyone identifying you based on this information is very low.

In addition to the planned use and sharing described above, we might remove any labels from your specimens and data that might identify you (i.e., anonymize them), and use them or share them with other researchers for future studies at the NIH or other places. When we or the other researchers use your anonymized specimens and data for these projects, there will be no way to know that they came from you. We want to make sure that you understand that this is a possibility if you participate in this study. Once we do this, we would not be able to remove your specimens or data from these studies or prevent their use in future studies because we would not be able to tell which specimens or data belong to you.

Risks of storage and sharing of specimens and data

When we store your specimens and data, we take precautions to protect your information from others who should not have access to it. When we share your specimens and data, we will do everything we can to protect your identity, for example, when appropriate, we remove information that can identify you. Even with the safeguards we put in place, we cannot guarantee that your identity will never become known or that no one will gain unauthorized access to your information. New methods may be created in the future that could make it possible to re-identify your specimens and data.

Can you change your mind about use and sharing for future research?

If you change your mind and do not want us to store and use your specimens and data for future studies, you should contact the study team. We will do our best to comply with your request but cannot guarantee that we will always be able to destroy your specimens and data. For example, if some research with your specimens and data is already complete, the information from that research may still be used. Also, if the specimens and data have been shared already, it might not be possible to withdraw them.

How long will your specimens and data be stored by the NIH?

Your specimens and data may be stored by the NIH indefinitely.

PAYMENT

Will you receive any type of payment for taking part in this study?

You will not receive any payment for taking part in this study.

REIMBURSEMENT

Will you receive reimbursement or direct payment by NIH as part of your participation?

On this study, the NCI will reimburse the cost for some of your expenses such as those for hotel, travel, meals. Some of these costs may be paid directly by the NIH and some may be reimbursed after you have paid. The amount and form of these payments are determined by the NCI Travel and Lodging Reimbursement Policy. You will be given a summary of the policy which provides more information.

If your travel to the NIH Clinical Center (e.g., flight, hotel) is arranged and paid for by the NIH, the agency making the reservations and their representatives will have access to your identifiable information.

COSTS

Will taking part in this research study cost you anything?

NIH does not bill health insurance companies or participants for any research or related clinical care that you receive at the NIH Clinical Center.

If some tests and procedures are performed outside the NIH Clinical Center, you may have to pay for these costs.

CONFLICT OF INTEREST (COI)

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

The NIH and the research team for this study are using PRGN-2009 developed by [redacted] through a collaboration between your study team and the company. The company also provides financial support for this study.

CLINICAL TRIAL REGISTRATION AND RESULTS REPORTING

A description of this clinical trial will be available on 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.

CONFIDENTIALITY PROTECTIONS PROVIDED IN THIS STUDY

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 NIH and other government agencies, like the Food and Drug Administration (FDA), which are involved in keeping research safe for people.
- National Institutes of Health Intramural Institutional Review Board
- The study Sponsor, NCI Center for Cancer Research or their agent(s)
- Qualified representatives from [redacted] the pharmaceutical company who produces PRGN-2009 and provides support for the study

The researchers conducting this study and the NIH follow applicable laws and policies to keep your identifying information private to the extent possible. However, there is always a chance that, despite our best efforts, your identity and/or information about your participation in this research may be inadvertently released or improperly accessed by unauthorized persons.

In most cases, the NIH will not release any identifiable information collected about you without your written permission. However, your information may be shared as described in the section of this document on sharing of specimens and data, and as further outlined in the following sections.

Further, the information collected for this study is protected by NIH under a Certificate of Confidentiality and the Privacy Act.

Certificate of Confidentiality

To help us protect your privacy, the NIH Intramural Program has received a Certificate of Confidentiality (Certificate). With this certificate, researchers may not release or use data or information about you except in certain circumstances.

NIH researchers must not share information that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings, for example, if requested by a court.

The Certificate does not protect your information when it:

1. is disclosed to people connected with the research, for example, information may be used for auditing or program evaluation internally by the NIH; or
2. is required to be disclosed by Federal, State, or local laws, for example, when information must be disclosed to meet the legal requirements of the federal Food and Drug Administration (FDA);
3. is for other research;
4. is disclosed with your consent.

The Certificate does not prevent you from voluntarily releasing information about yourself or your involvement in this research.

The Certificate will not be used to prevent disclosure to state or local authorities of harm to self or others including, for example, child abuse and neglect, and by signing below you consent to those disclosures. Other permissions for release may be made by signing NIH forms, such as the Notice and Acknowledgement of Information Practices consent.

Privacy Act

The Federal Privacy Act generally protects the confidentiality of your NIH medical information that we collect under the authority of the Public Health Service Act. In some cases, the Privacy Act protections differ from the Certificate of Confidentiality. For example, sometimes the Privacy Act allows release of information from your record without your permission, for example, if it is requested by Congress. Information may also be released for certain research purposes with due consideration and protection, to those engaged by the agency for research purposes, to certain federal and state agencies, for HIV partner notification, for infectious disease or abuse or neglect reporting, to tumor registries, for quality assessment and medical audits, or when the NIH is involved in a lawsuit. However, NIH will only release information from your medical record if it is permitted by both the Certificate of Confidentiality and the Privacy Act.

RESEARCH-RELATED INJURIES

The NIH 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 NIH, the NIH Clinical Center, or the Federal Government. However, you have the right to pursue legal remedy if you believe that your injury justifies such action.

PROBLEMS OR QUESTIONS

If you have any problems or questions about this study, about your rights as a research participant, or about any research-related injury, contact the Principal Investigator, Charalampos Floudas, MD, [redacted]. You may also call the NIH Clinical Center Patient Representative at [redacted], or the NIH Office of IRB Operations at [redacted] if you have a research-related complaint or concern.

CONSENT DOCUMENT

Please keep a copy of this document in case you want to read it again.

Adult Research Participant: I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I consent to participate in this study.

Signature of Research Participant	Print Name of Research Participant	Date

Investigator:

Signature of Investigator	Print Name of Investigator	Date

Witness should sign below if either:

1. **A short form consent process has been used to enroll a non-English speaking subject or**
2. **An oral presentation of the full consent has been used to enroll a blind or illiterate subject**

Signature of Witness	Print Name of Witness	Date

NIH ADMINISTRATIVE SECTION TO BE COMPLETED REGARDING THE USE OF AN INTERPRETER:

____ An interpreter, or other individual, who speaks English and the participant's preferred language facilitated the administration of informed consent and served as a witness. The investigator obtaining consent may not also serve as the witness.

____ An interpreter, or other individual, who speaks English and the participant's preferred language facilitated the administration of informed consent but did not serve as a witness. The name or ID code of the person providing interpretive support is: _____.