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STUDY TITLE: Phase I/II Trial of HPV Vaccine PRGN-2009 Alone or in Combination with Anti-PD-L1/TGF-β trap (M7824) in Subjects with HPV Associated Cancers

STUDY SITE: NIH Clinical Center

Cohort: *Phase I Participants*

Consent Version: *04/25/2023*

WHO DO YOU CONTACT ABOUT THIS STUDY?

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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 make a decision can be found in other sections of the document. Taking part in research at the NIH is your choice.

This study consists of 2 phases.

You are being asked to take part in the Phase I part of the study because you have locally advanced or metastatic HPV associated cancer which has come back after treatment. If you have not had treatment it is because you were not able to take the standard treatment or you decided against it.

The purpose of Phase I part of research study is to determine a safe dose of HPV vaccine alone or HPV vaccine in combination with M7824. A second purpose is to find out if giving you this therapy can shrink your tumor.

Depending on when you enter the Phase I part of the study, you will have treatment with HPV vaccine alone (Group A) or HPV vaccine + M7824 (Group B).

Group A: The first few participants will receive a low dose of HPV vaccine. If we find that this dose is safe, the next set of participants will receive a higher dose of the vaccine. If that dose is well tolerated, another set of participants will be enrolled in Group B.

Group B: This group of participants will receive the HPV vaccine at the dose found to be safe in Group A along with M7824 at the standard dose.

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

- M7824 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 your cancer than when they work alone.

The use of HPV vaccine and M7824 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 HPV associated cancers. However, the FDA has given us permission to use the combination of HPV vaccine and M7824 in this study.

M7824 has been tried in other types cancers. Recently, the manufacturer of the drug closed 3 large studies because the drug was not shown to help those patients more than standard therapies. In addition, in some cases it seemed like the drug might make the cancer grow faster. However, the type of cancer treated in those studies was not the same as your cancer.

There are other drugs that may be used to treat your disease and these can be given by your regular cancer doctor if you are not in this study. For example: Standard of care chemotherapy or immunotherapy may be available.

Side effects can occur with immunotherapy drugs as explained later in the consent. By participating in this study, you will be at risk of experiencing these side effects.

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

- Once you meet the study requirements to enroll in Phase I, you will receive immunotherapy drugs as follows:
  - HPV vaccine will be given by injection under the skin on Day 1, Day 15, and Day 29, followed by a booster vaccine every 4 weeks.
  - M7824 will be given by intravenous infusion (a small catheter is inserted into a vein allowing the solution to be given) every two weeks. The infusion will take approximately one hour, but could take more or less time.
  - Every 4 weeks, HPV vaccine booster doses will be matched with an M7824 infusion. When possible, vaccine will be given first followed by M7824.
- Each treatment will be given in the Oncology Outpatient Center and will take approximately 2-4 hours.
- You will be seen regularly during the study. 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 samples from you (such as blood and tumor biopsies) for both clinical and research purposes.
- About four weeks after your study therapy has ended, you will be seen in the clinic and possibly have more labs. These visits are important for your safety and if you cannot come to the NIH in person, you will be contacted by phone for follow-up.

- We will contact you for long term follow-up every year, for the rest of your life, to ask about any adverse events, further treatment of your tumor, and your 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:
  - Anemia (low number of red blood cells)
  - Decreased appetite
  - Fatigue
  - Itching
  - Shortness of breath
  - Constipation (difficulty passing stools)
  - Nausea (feeling sick to the stomach)
  - Fever
  - Decreased muscle strength
  - Diarrhea (frequent loose, watery stools)
  - Abdominal pain
  - Vomiting
  - Cough
  - Headache
  - Bleeding from the nose, gums, tumor, and other potentially fatal bleeding
  - Rash
  - Abnormal liver function tests
  - Build-up of fluid in the body causing swelling

It is possible that the anemia and/or bleeding may be so severe that you require a blood transfusion. You cannot join this study if you are not willing to have a blood transfusion.

A more complete list of possible side effects is described later in this consent. It is important that you read and understand the possible risks.

Just as we do not know what side effects you might have, we cannot know if you may benefit from taking part in this study. If you do not benefit, 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 more about the research study. This information should be considered before you make your choice. Members of the study team will talk with you about the information described in this document. Some people have personal, religious, or ethical beliefs that may limit the kinds of medical or research intervention in which they would want to participate. Take the time needed to ask any questions and discuss this study with NIH staff, and with your family, friends, and personal health care providers.

If the individual being asked to participate in this research study is not able to give consent to be in this study, you are being asked to give permission for this person as their decision-maker. The term "you" refers to you as the decision-maker and/or the individual being asked to participate in this research, throughout the remainder of this document.

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?

This study has two phases.

The purpose of the Phase I part of this research study is to determine a safe dose of HPV vaccine alone or HPV vaccine in combination with M7824. A second purpose is to find out if giving you this therapy can shrink your tumor.

You are being asked to take part in the Phase I part of the study because you have been diagnosed with a locally advanced or metastatic HPV associated cancer.

The use of HPV vaccine and M7824 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 HPV associated cancers. However, the FDA has given us permission to use the combination of HPV vaccine and M7824 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

To determine if you can be a part of this study, you will need to have the following tests and procedures. These may be done under a separate protocol:

- Medical history and physical examination including height, weight, and vital signs;
- CT scan of the brain, chest, abdomen and pelvis;
- Routine blood tests;
- EKG;
- For skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion;
- Pregnancy test for women who are able to have children;
- Hepatitis B and C screening tests;
- HIV screening test;
    - As part of this study, we will test you for infection with HIV, the virus that causes 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.
- Urine tests;

- Confirmation of your disease. If there is no available tumor sample or pathology report, a biopsy will be performed to confirm the diagnosis.

During the study

Once we know that you are eligible and you sign the consent document agreeing to participate in the study, you may need to have some of the tests that were done at screening repeated depending on how much time has passed. Your study team will let you know if any of the following tests need to be repeated on Week 1 Day 1.

- Medical history and physical examination including height, weight, and vital signs;
- CT scan of the chest, abdomen and pelvis and/or MRI;
- Brain CT/MRI;
- Routine blood and urine tests;
- Pregnancy test for women who are able to have children (within 5 days before starting drug treatment);
- Hepatitis B and C screening tests;
- HIV screening test;
- EKG to check your heart;
- Assessment of hypersensitity, if required;
- For skin lesions: color photography, if needed;
- Tumor markers.

During your participation you will receive the HPV vaccine alone or in combination with M7824 as explained in Key Information section above.

- If you are enrolled in Group A, you will receive the HPV vaccine by injection under the skin on Day 1, Day 15, and Day 29, followed by a booster vaccine every 4 weeks for up to one year. If you are in Group B, you will receive the HPV vaccine along with M7824 by IV infusion every two weeks for up to a year.
- M7824 infusion will take approximately one hour, but could take more or less time. Before your M7824 infusion you may receive standard pre-medication of an antihistamine and acetaminophen (Tylenol).

We will continue to take assessments, such as physical exam, weight, vital signs, EKG, collection of blood for routine lab testing, tumor markers, pregnancy test for women of childbearing age, and scans for the evaluation of your tumor, during your participation.

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. The samples are being tested to look at the effects of therapy on your immune system and markers of tumor activity, including collecting and testing tumor cells, as well as development of anti-vector antibodies (AVA) and anti-drug antibodies (ADA) in response to the therapy. The pharmacokinetics (PK) of bintrafusp alfa in your blood will also be tested.

The samples for these studies include:

- Blood Tests: When possible, research blood will be collected at Week 1 Day 1, and at Weeks 3, 5, and 11. Additional research blood (about 4 tablespoons) may be collected every 8 weeks after that.
- Tumor Biopsy (optional): Tissue sample will be collected at Week 1 Day 1 or Week 9. Biopsies will likely be CT guided.

In this study we will perform genetic testing on your RNA. RNA (ribonucleic acid) carries instructions from your DNA (deoxyribonucleic acid) to the parts of the cells that makes proteins. We will perform limited genetic testing on certain immune cells in your blood and tumor samples to characterize changes in the RNA of a particular molecule located on the immune cell. We will perform further genetic testing on your blood samples, looking at how much RNA you have for certain panels genes. This helps us to learn how active the genes are.

When you are finished with treatment

End of Treatment Visit

If you stop participation in the study before the completion of one year of treatment, then you will be asked to come into the clinic on the day of or within 7 days of the decision to stop treatment for the following tests and procedures: physical examination including weight, and vital signs; EKG; routine blood tests to measure blood chemistry and complete blood count; pregnancy test if you are a woman who can have children; and scans if you stop study therapy before your disease worsens.

Safety Visit

After your treatment ends or if you stop participation in the study for any reason you will be asked to come into the clinic for a 28 day follow-up visit or telephone call following your last dose of study drug(s).

During the visit the following tests and procedures will be given: physical examination including weight and vital signs; EKG; and routine blood tests; and pregnancy test if you are a woman who can have children.

Long Term Follow-up

We will also contact you for long term follow-up every year, for the rest of your life.

If your disease has progressed while being treated then you will be followed by phone or email for any adverse events, further treatment of your tumor, and your survival.

If your disease did not progress while being treated then you will receive tumor scans until progression of your disease and will be followed by phone or email for any adverse events, further treatment of your tumor, and your survival. If you completed one year of treatment on this study then you may be asked to complete an additional year of treatment at the time of your disease progression. After that one year a follow-up visit may be required if determined by your study doctor.

HOW LONG WILL THE STUDY TAKE?

If you agree to take part in this study, the treatment portion is expected to last for about one year for Phase I. After the treatment part is completed, we will continue to follow you until the study ends or you decide to stop participating.

HOW MANY PEOPLE WILL PARTICIPATE IN THIS STUDY?

We plan to have approximately 22 people participate in the Phase I part of the study and 22 people in the Phase II part of the study at the NIH.

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

Risks from Study Therapy

Side Effects of HPV Vaccine (PRGN-2009)

This is a first in human study with PRGN-2009. Possible side effects may include injection site reaction, fever, flu like symptoms (e.g., fatigue, headache, muscle aches), poor appetite, increase in blood sugar, and skin rash.

Side Effects of M7824

The M7824 used in this study may affect how different parts of your body work such as your liver, kidneys, heart, and blood. The study doctor will be testing your blood and will let you know if changes occur that may affect your health.

Below we list the most common and the most serious side effects that researchers know about. There might be other side effects that researchers do not yet know about. If important new side effects are found, the study doctor will discuss these with you.

Common side effects (occurring in more than 5% of patients):

- Fatigue (tiredness and lack of energy)
- Nausea
- Diarrhea
- Constipation
- Vomiting
- Swelling of your lower legs or hands
- Fever
- Decreased appetite
- Loss of body fluids (dehydration)
- Skin growths called keratoacanthomas that resemble skin cancer. These usually go away after treatment and can leave a scar.
- Rash, blisters, skin discoloration and other skin abnormalities
- Bleeding has been frequently observed in patients receiving M7824. Patients may experience bleeding in different organs such as gum, nose, ears, eyes,vagina, breast, blood in the urine stool or bleeding in the internal organs or skull, coughing up or vomiting blood. Occasionally, this bleeding can be serious and potentially life threatening and require you to receive a blood transfusion. If you experience any bleeding on this

trial, please tell the study team immediately. Tell your doctor if you've had a life-long problem of frequent or excessive bleeding or bruising, or if you take aspirin or prescription medication to thin your blood.
- Shortness of breath
- Cough
- Anemia – low number of red blood cells that can cause tireness and shortness of breath. May require a blood transfusion.
- Abdominal pain
- Headache
- Itching

Occasional side effects (occurring in less than 5% of patients):

- Chills (feeling cold)
- Blood clots that form throughout the body, blocking small blood vessels. Symptoms may include chest pain, shortness of breath, leg pain, problems speaking, or problems moving parts of the body
- Easy bruising
- Reaction to other drugs such as rash, anaphylaxis, and changes in blood
- Infusion-related reaction, including dizziness or fainting (low blood pressure), flushing, rash, fever, shortness of breath or sick to your stomach, or pain at the site of infusion. Although usually reversible with treatment, it can be severe or life threatening.
- Back pain
- Cancerous growth on the skin that can be removed
- Stroke
- Slow wound healing
- Thickening of the skin, nails

In addition to the above, we have seen a few cases of nodular regenerative hyperplasia. This is when small growths, or nodules, occur in the liver. These usually do not cause symptoms, but can occasionally be associated with high blood pressure in the vein to the liver which could over time lead to liver damage.

Allergic reactions or reactions in the context with the infusions might occur during treatment.

Although M7824 is a fully human protein the risk cannot be completely excluded. In general, these reactions are mild to moderate and can be handled with appropriate drugs, but in very rare cases severe to 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 acetaminophen 60 to 120 minutes before the 1st and 2nd infusions.

In addition, immune-mediated side effects might be possible. These adverse events are caused by over activity of your body's immune-system caused by M7824. The immune system normally protects you from infections and foreign substances, such as cancer. If the immune system is

overactive, it may think that parts of the body, including vital organs, are foreign substances and attack them.

Examples of these side effects are:

- Inflammation in the lungs (pneumonitis): symptoms may include but are not limited to a new or worsening cough, shortness of breath possibly with fever. Preliminary data suggested that there may be the tendency of higher frequency and severity in Japanese patients compared with non-Japanese patients: tell your study doctor right away if you have any of these symptoms as it may need to be treated urgently.
- Hypothyroidism (decreased function of the thyroid gland)
- Hyperthyroidism (increased function of thyroid gland)
- Thyroiditis (inflammatory disease of the thyroid gland)
- You may develop inflammation of the liver called hepatitis. Signs and symptoms of this include yellowing of the skin or whites of the eyes, dark urine, severe nausea and vomiting, pain in the upper right side of your abdomen, skin itchiness, not feeling hungry and bleeding or bruising more easily than normalThrombocytopenia (decrease of the blood platelets).
- Uveitis (inflammation in the eyes)
- Diabetes mellitus (high blood sugar levels)
- Problems with your adrenal glands (Adrenal Insufficiency): may cause stomach pains, vomiting, muscle weakness and fatigue, depression, low blood pressure, weight loss, kidney problems, and changes in mood and personality. These complications may be permanent and may require hormone replacement.
- Myositis (inflammation of the muscles characterized by pain and tenderness)
- Inflammation of the intestine (colitis). It may cause abdominal pain and diarrhea with or without blood. Fever may be present. It may require you to receive additional fluids. If left untreated, in rare occasions this may lead to a tear in the wall of the intestine which can be serious and life threatening.
- Autoimmune encephalitis is a type of brain inflammation where the body's immune system attacks healthy cells and tissues in the brain or spinal cord.
- Myocarditis (inflammation of the heart muscle)
- Pemphigoid (fluid-filled blisters that can be itchy)
- Kidney problems: you may have an increase of creatinine levels in a blood test (creatinine is a protein marker that measures kidney function) but not have any symptoms or feel unwell. Uncommonly a patient may experience nephritis which is an inflammation of the kidneys that stops the kidneys from working properly.
- Problems with the pituitary gland (hypopituitarism): Hypopituitarism refers to decreased output of hormones from the pituitary gland in the brain and may be caused by inflammation of the pituitary gland (hypophysitis). Symptoms may include headaches, thirstiness, and trouble seeing or double vision, leakage of breast milk or irregular periods in women. These complications may be permanent and may require hormone replacement.
- Pancreatitis (inflammation of the pancrease)

- Liver problems: Increases in the blood level of substances called enzymes found within your liver cells. The enzyme changes are unlikely to make you feel unwell, however, if these blood enzyme levels become very high, your study doctor may need to stop the study medication.
- Nervous system problems: symptoms can include unusual weakness of legs, arms, or face, numbness, or tingling in hands or feet. In rare situations, there is the potential for the inflammation of the nervous system to be severe.

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

Other Risks

Risk from Blood Collection

Risks of blood draws include pain and bruising in the area where the needle is placed, lightheadedness, and rarely, fainting. When large amounts of blood are collected, low red blood cell count (anemia) can develop.

Risks from Biopsy

Care will be taken to minimize risks that may happen during collection of a tumor sample. This procedure usually causes only brief discomfort at the site from which the biopsy is taken. You may experience some bruising around the biopsy site. Rarely, infection or bleeding may occur at the needle site.

Tumor biopsies will be done by a specialist using the CT scanner or ultrasound machine to guide the biopsy needle into the tumor to ensure accuracy. To collect the optional research biopsies, you may be exposed to 2 CT scans. Your radiation exposure from this procedure is below the guidelines allowed for research subjects at the NIH. See below for more details.

CT Scan Risk

CT scans create low levels of radiation, which has a small potential to cause cancer and other defects. However, the risk associated with one scan is small.

Risks Due to Contrast Agents for CT

You may receive a contrast agent as part of your CT 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.

MRI

Magnetic resonance imaging (MRI) uses a strong magnetic field and radio waves to take pictures of the body. If you have a history of metastases to your brain or if we are concerned that you may have metastases to your brain, we will obtain pictures of your brain for this study. The MRI scanner is a metal cylinder surrounded by a strong magnetic field. During the MRI, you will lie on a table that can slide in and out of the cylinder. We will place soft padding or a coil around your head. You will be in the scanner about 30 minutes. You may be asked to lie still for up to 30 minutes at a time. While in the scanner you will hear loud knocking noises, and you will be fitted with

earplugs or earmuffs to muffle the sound. You will be able to communicate with the MRI staff at all times during your scan, and you may ask to be moved out of the machine at anytime.

It is very important for the experiment that you do not move your head or body inside the scanner. We will use padding around your head to help keep it in place.

We may place a bar in your mouth to help keep your head still.

Risks for MRI

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.

Risks of Gadolinium enhanced MRI

During part of the MRI you will receive gadolinium, a contrast agent, through an intravenous (iv) catheter. It will be done for 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. We will also give you additional information called a "Medication Guide." Upon request, we will give you individual information about retained gadolinium we see on your studies.

What are the risks related to pregnancy?

If you are able tobecome pregnant, we will ask you to have a pregnancy test before starting this study. You will need to practice an effective form of birth control before starting study treatment, during study treatment, and for 2 months after you finish study treatment (the restricted period).

If you become pregnant, there may be unknown risks to the fetus or unborn child, or risks that we did not anticipate. There may be long-term effects of the treatment being studied that could increase the risk of harm to a fetus. You must tell the study doctor if your birth control method fails during the restricted period. If you think or know you have become pregnant during the restricted period., please contact the study team as soon as possible.

If you are a sexually active person with a partner able to become pregnant, it is important that your partner not become pregnant during the restricted period. There may be unknown risks to the fetus or risks we did not anticipate. You and your partner must agree to use birth control if you want to take part in this study. If you think your partner has become pregnant during the restricted period, please contact the study team as soon as possible. If you and your partner plan for your partner to become pregnant after the restricted period, please discuss this with the study team.

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 CT scans and CT guided biopsies (optional). The amount of radiation exposure you will receive from these procedures is equal to approximately 10.6 rem. A rem is a unit of absorbed radiation.

Note: The 2 CT guided biopsies are optional and depend on your decision to agree to the biopsies and their location with your study doctor.

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 scans and CT guided biopsies that you get in this study will expose you to the roughly the same amount of radiation as 35.3 years' worth of background radiation. Being exposed to too much radiation can cause harmful side effects such as an increase in the risk of cancer. The risk depends

on how much radiation you are exposed to. Please be aware that about 40 out of 100 people (40%) will get cancer during their lifetime, and 20 out of 100 (20%) will die from cancer. The risk of getting cancer from the radiation exposure in this study is 1.1 out of 100 (1.1%) and of getting a fatal cancer is 0.5 out of 100 (0.5%).

You may not participate in this study if you are pregnant. If you are able to become pregnant, we will perform a pregnancy test before exposing you to radiation. You must tell us if you may have become pregnant within the previous 14 days because the pregnancy test is unreliable during that time.

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.

WHAT ARE THE BENEFITS OF BEING IN THE STUDY?

You might not benefit from being in this study.

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

There is a need for new treatments in patients with advanced 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 combination 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 be treated with surgery, radiation or with drugs already approved by the FDA for your disease;
- choose to take part in a different study, if one is available;
- choose not to be treated for cancer but you may want to receive comfort care to relieve symptoms.

You should discuss with your doctor your other choices and their risks and benefits.

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.

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 HPV vaccine, and/or M7824 becomes 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 Precigen, Inc., EMD Serono, Inc., or designated representatives.

STORAGE, SHARING AND FUTURE RESEARCH USING YOUR SPECIMENS AND DATA

Will your Specimens or Data be Saved for Use in Other Research Studies?

As part of this study, we are obtaining specimens and data from you. We will remove all the identifiers, such as your name, date of birth, address, or medical record number and label your specimens and data with a code so that you cannot easily be identified. However, the code will be linked through a key to information that can identify you. We plan to store and use these specimens and data for studies other than the ones described in this consent form that are going on right now, as well as studies that may be conducted in the future. These studies may provide additional information that will be helpful in understanding HPV associated cancers 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 coded specimens and data to be stored and used for future research as described above.

_____ Yes _____ No

Initials Initials

Will Your Specimens or Data Be Shared for Use in Other Research Studies?

We may share your coded specimens and data with other researchers. If we do, while we will maintain the code key, we will not share it, so the other researchers will not be able to identify you. They may be doing research in areas similar to this research or in other unrelated areas. These researchers may be at NIH, other research centers and institutions, orcommercial entities.

I give permission for my coded specimens and data to be shared with other researchers and used by these researchers for future research as described above.

_____ Yes _____ No

Initials Initials

If you change your mind and do not want us to store and use your specimens and data for future research, you should contact the research team member identified at the top of this document. 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 has already been completed, the information from that research may still be used. Also, for example, if the specimens and data have been shared already with other researchers, it might not be possible to withdraw them.

In addition to the planned use and sharing described above, we might remove all identifiers and codes from your specimens and data and use or share them with other researchers for future research at the NIH or other places. When we or the other researchers access your anonymized data, there will be no way to link the specimens or data back to you. We will not contact you to ask your permission or otherwise inform you before we do this.We might do this even if you answered "no" to the above questions. If we do this, we would not be able to remove your specimens or data to prevent their use in future research studies, even if you asked, because we will not be able to tell which are your specimens or data.

NIH policies require that your clinical and other study data be placed in an internal NIH database that is accessible to other NIH researchers for future research. These researchers will not have access to any of your identifiers, such as your name, date of birth, address, or medical record number; and your data will be labeled with only a code. We cannot offer you a choice of whether your data to be placed in this database or not. If you do not wish to have your data placed in this database, you should not enroll in this study.

Will Your Genomic Data Be Shared Outside of This Study?

As part of this research study, we will put your genomic data in a large database for broad sharing with the research community. These databases are commonly called data repositories. The information in this database will include but is not limited to genetic information, race and ethnicity and sex. If your individual research data are placed in one of these repositories, they

will be labeled with a code and not with your name or other information that could be used to easily identify you, and only qualified researchers will be able to access them. These researchers must receive prior approval from individuals or committees with authority to determine whether these researchers can access the data.

NIH policies require that genomic data be placed in a repository for sharing. Therefore, we cannot offer you a choice of whether your data will be shared. If you do not wish to have your data placed in a repository, you should not enroll in this study.

How Long Will Your Specimens and Data be Stored by the NIH?

Your specimens and data may be stored by the NIH until they are no longer of scientific value or if you withdraw consent for their continued use, at which time they will be destroyed. Your specimens and data may be stored by the NIH indefinitely.

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 that 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.

COMPENSATION, REIMBURSEMENT, AND PAYMENT

Will you receive compensation for participation in the study?

Some NIH Clinical Center studies offer compensation for participation in research. The amount of compensation, if any, is guided by NIH policies and guidelines.

You will not receive compensation for participation in this study.

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

Some NIH Clinical Center studies offer reimbursement or payment for travel, lodging or meals while participating in the research. The amount, if any, is guided by NIH policies and guidelines.

On this study, the NCI will cover the cost for some of your expenses. 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.

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

CONFLICT OF INTEREST (COI)

The National Institutes of Health (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 National Institutes of Health and the research team for this study have a patent for any drug(s) dually targeting a blockade of PD-L1 and TGF beta in HPV positive malignancies. This is the mechanism for one of the drugs being looked at in this study. This means it is possible that the results of this study could lead to payments to NIH. By law, the government is required to share such payments with the employee inventors. You will not receive any money from the development of drugs dually targeting PD-L1 and TGF beta in HPV positive malignancies.

The NIH and the research team for this study are using:

- HPV vaccine (PRGN-2009) developed by Precigen, Inc., and
- M7824 developed by EMD Serono, Inc.

through a joint study with your study team and these companies. These companies also provide 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

Some of your health information, and/or information about your specimen, from this study will be kept in a central database for research. Your name or contact information will not be put in the database. Your test results will be identified by a unique code and the list that links the code to your name will be kept separate from your sample and health information. Your information may be given out if required by law. For example, certain states require doctors to report to health boards if they find a disease like tuberculosis. However, the researchers will do their best to make sure that any information that is released will not identify you.

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 (Center for Cancer Research) or their agent(s)
- Qualified representatives from Precigen, Inc., the pharmaceutical company who produces HPV vaccine, or their agent(s).
- Qualified representatives from EMD Serono, Inc., the pharmaceutical company who produces M7824, or their agent(s).

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 the 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); or
3. is for other research; or
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 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 medical 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.

POLICY REGARDING 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, or about your rights as a research participant, or about any research-related injury, contact the Principal Investigator, Charalampos Floudas, MD, charalampos.floudas@nih.gov, 240-858-3032. You may also call the NIH Clinical Center Patient Representative at 301-496-2626, or the NIH Office of IRB Operations at 301-402-3713, 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

Legally Authorized Representative (LAR) for an Adult Unable to Consent: I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I am legally authorized to make research decisions on behalf of the adult participant unable to consent and have the authority to provide consent to this study. As applicable, the information in the above consent was described to the adult participant unable to consent who agrees to participate in the study.

Signature of LAR	Print Name of LAR	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 ubject 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: _____.