PRINCIPAL INVESTIGATOR: Andrea B. Apolo, M.D

STUDY TITLE: A Phase II Study of Bintrafusp alfa (M7824) in Checkpoint Inhibitor Naïve and Refractory Subjects with Urothelial Carcinoma

STUDY SITE:	NIH Clinical Center
Cohort:	Affected Patients
Consent Version:	June 23, 2021

WHO DO YOU CONTACT ABOUT THIS STUDY?

Study PI: Andrea B. Apolo, M.D.
Phone: 301-480-0536
Email: andrea.apolo@nih.gov

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 urothelial cancer that has spread to other parts of your body and you have been previously treated with chemotherapy or immunotherapy.

The purpose of this study is to learn if giving M7824 could help your immune system fight the cancer.

M7824 is a drug that blocks pathways that cancer cells use to prevent your immune system from fighting your cancer.

The use of M7824 in this study is considered investigational, which means that this drug has not been approved by the U.S. Food and Drug Administration (FDA) to treat urothelial cancer However, the FDA has given us permission to use M7824 in this study.

There are other standard of care drugs that can be given by your regular cancer doctor and could be more effective to treat your disease. If you decide to participate in this study, you will not be able to receive any of these conventional cancer treatments. Depending on your disease and prior treatments, these drugs could include chemotherapy and/or FDA approved immune check-point inhibitors ("immunotherapy").

Standard chemotherapies that are platinum-based (such as cisplatin or carboplatin) or taxane based (such as paclitaxel, abraxane or docetaxel) are some possible treatments that you could receive. Standard platinum-taxane-based chemotherapies are known to cause changes in blood counts, nausea, vomiting, fatigue, and neuropathy (tingling and/or numbness most often in the fingers and toes).

If you have not already received immunotherapy, you may be eligible to receive it as a standard treatment. This includes FDA approved drugs like atezolizumab, avelumab, durvalumab, nivolumab, and pembrolizumab. These drugs alter the immune system and may lead to known autoimmune side effects like fatigue, skin problems, diarrhea, liver damage, and lung inflammation.

The treatment being given in this study and the side effects are different than if you were to receive standard care.

M7824 is a new immunotherapy drug and although it may cause similar side effects of other immunotherapy agents, it has also been found to cause additional skin problems, different problems with the immune system, low red blood cell count (anemia) and bleeding. 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.

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

- M7824 is given as an IV (intravenous) infusion. A small plastic tube is put into a vein in your arm and the medication is given once every two weeks.
- You will be seen in the NIH Clinical Center by your study team every 2 weeks while you are receiving treatment. These clinic visits will take 2-4 hours. The treatments will be given in the Oncology Outpatient Center every two weeks during the treatment portion of the study and those visits will take 4-6 hours. Treatment will continue until your cancer worsens, you develop unacceptable side effects or you decide to stop receiving the study treatment.
- You will have clinical, laboratory, and imaging tests to see how you are doing and to assess your disease. We will also collect required samples from you (such as: blood and tissue samples) for both clinical and research purposes.
- After the study treatment has ended, you will be seen in the NIH Clinical Center by your study team after 30 days from the last dose of drug and then you will be followed indefinitely in clinic or over phone/email every 12 weeks. You will have tests done (physical exams and blood work) either at NIH or by your local provider to see how you are doing and to see how your disease is responding.

As described above and later in more detail in this consent form, you may experience side effects from taking part in this study. Some can be mild or very serious, temporary, long-lasting, or permanent, any may include death.

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 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.

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

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 main purpose of this research study is to learn if giving M7824 could help your immune system's ability to fight urothelial cancer.

We are asking you to join this research study because you have metastatic urothelial cancer that has not responded to previous treatment with chemotherapy and/or immunotherapy

M7824 is considered investigational, which means that it has not been approved by the U.S. Food and Drug Administration (FDA) to treat urothelial cancer. Prior clinical studies with M7824 have helped researchers learn about the recommended doses that are safe.

WHAT WILL HAPPEN DURING THE STUDY?

Before you begin the study

Before beginning the study, you will be evaluated by a physician investigator, as well as other members of the research team for eligibility to participate in the study. We will discuss your medical history in detail and draw blood from a vein to perform laboratory tests to help determine whether you are eligible to participate. We will also need a small sample of tissue (biopsy) from your cancer in order to confirm your diagnosis. These tests and/or procedures will help your doctor verify whether you can participate. This is called screening. The exams, tests, and procedures you will have are

part of the usual approach for people who have genitourinary cancers. We will discuss these tests and the reasons they are required if you need to have them. Most scans must be performed within 21 days before enrollment. Briefly, these tests, which will be performed under a separate protocol include:

- Confirmation of diagnosis (You must provide a sample tumor tissue for formal evaluation by the NCI Laboratory of Pathology. The tissue may be from a previous surgery or biopsy. If none is available, we will ask you to have a biopsy to provide a fresh sample).
- Medical history and physical examination including weight, height and vital signs
- Blood and urine lab tests
- Pregnancy test in women who can have children. Pregnant women will not be allowed on study.
- CT Scans or MRI if CT scans cannot be done
- Electrocardiogram (ECG)
- Tests for certain infections (Hepatitis B, Hepatitis C)

During the study

In this study, you will undergo a series of treatment cycles, each lasting 28 days.

You will need to make several visits to the study center for testing during the treatment period. It is important that you come to all of these scheduled visits.

At the visit to the study center after you first join the study, the study doctor will do the following tests and procedures. Some tests or procedures done at screening may not be repeated on this day. Your doctor will let you know which ones.:

- Perform a complete physical examination
- Assess your Eastern Cooperative Oncology Group (ECOG) performance status. ECOG measures your ability to perform your normal activities.
- Record your vital signs (blood pressure, heart rate, body temperature, and breathing rate)
- Pregnancy test, if applicable
- Routine blood tests
- M7824 will be given once every 2 weeks through an IV (infusion). This procedure takes about 1 hour.
- For the prevention of infusion-related adverse effects and possible allergic reactions, you will receive an antihistamine drug (e.g. Benadryl) and an anti-inflammatory drug (e.g. acetaminophen) before the first 2 infusions of M7824. Based on how your body reacts to the first 2 infusions, the study doctor will see if you will need to continue receiving these medication drugs before your other infusions.
- You will continue to be treated with M7824 until your disease gets worse, you have unacceptable side effects or you decide to stop receiving the study treatment.

Follow-up tests

Every two weeks:

- Medical history and physical exam

- Blood tests
- Vital signs

Every 4 weeks:

- Pregnancy test, if you are a woman who could possibly become pregnant

Every 8 weeks

- Imaging scans to look at tumor growth (CAT scans)

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. The samples are being collected to look at the effects of therapy on your immune system and markers of tumor activity, including collecting and testing tumor cells. Unless noted otherwise below, the samples will be collected at least once each cycle and at the time your disease responds to treatment or gets worse (required), and at the end of treatment (optional).

Research imaging:

- Whole body MRI (also called diffusion weighted MRI or DW MRI) done before you start treatment at and at the start of cycle 3

Research samples include:

- blood (around 2 cups in the first 8 weeks and then about 1 cup every 8 weeks after that while on treatment)
- tissue (collected before you start treatment and at the start of cycle 3 (required, if your study doctor thinks it is feasible) and at your end of treatment visit - optional)

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 your DNA, we may use do what is called “whole genome sequencing” and “whole exome sequencing.” This where we will do special tests in the lab to look at the entire sequence, or order, of how your DNA is put together. This is what makes you unique.

To determine which parts of the DNA have mutated, we will compare the DNA in your tumor cells to DNA from your normal cells. We will then analyze the results from similar tumors to see if there are any changes in the DNA that are common to a particular type of tumor. 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), xenograft studies

(placing or growing cells in another animal, such as mice), 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 sensitive 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."

End of treatment visit

When you stop taking the study drug for any reasons, you will be asked to return to the study center for the end of treatment visit. This end of treatment visit should occur within 30 days after you stop taking the study drugs and, if possible, prior to starting any new therapy for your cancer.

At this visit, the study doctor/study team will do the following:

- Perform a complete physical examination and medical history
- Record your vital signs (blood pressure, heart rate, body temperature, and breathing rate) and body weight.
- EKG
- CT scans
- Collect blood (around ¼ cup) for safety laboratory assessments and research studies.
- Collect a urine sample
- Collect tissue samples (optional) for post-treatment research studies.

Long-term follow-up visit

You will be followed every 12 weeks in the clinic or by telephone/email for review of survival status, adverse events and information about new anti-cancer therapy you may have started. The study doctor will continue to follow-up with you indefinitely.

HOW LONG WILL THE STUDY TAKE?

You will continue to receive the study drug (in repeated 28-day cycles) until the cancer worsens, you have unacceptable side effects, you decide to no longer take part in the study or your study doctor decides it is no longer suitable for you to continue.

HOW MANY PEOPLE WILL PARTICIPATE IN THIS STUDY?

We plan to have approximately 75 people participate in this study at the NIH.

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

There are risks, discomforts, and inconveniences associated with any research study. These deserve careful thought. You should talk with the investigator if you have any questions.

It is probable that you will experience some of the side effects listed, but it is unlikely that you will experience all of them. You will be watched closely, and we will give you medicines to try and prevent or reverse the side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or very serious. In some cases, side effects can be serious, long

lasting, or may never go away. We will tell you if we learn any new information that may affect your health, welfare, or decision to stay in this study. You should talk to your study doctor about any side effects that you have while taking part in the study.

M7824

Common (occurring in more than 5 % of patients)

- Tiredness
- 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
- Shortness of breath
- Cough
- Anemia (low number of red blood cells that can cause tiredness and shortness of breath. May require a transfusion)
- Abdominal pain
- Headache
- Itching
- Bleeding has been frequently observed in patients receiving M7824. Patients may experience bleeding in different organs, such as gums, 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.

Occasional (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
- Certain type of a skin cancer
- Abdominal pain
- Non-cardiac chest pain
- Anemia or low blood cell count
- Allergic reactions or reactions related to the infusions might occur during treatment. Usually, these reactions are mild to moderate and can be treated with drugs, but could also be severe to life-threatening which could require advanced cardiac life support and even fatal reactions might occur.

  For the prevention of infusion-related side effects and possible allergic reactions you will receive of an antihistamine drug (Benadryl® or similar) and acetaminophen (Tylenol® or similar) 30 to 60 minutes before the first 2 infusions of M7824. Based on how your body reacts to the first 2 infusions, the study doctor will see if you will need to continue receiving these medication drugs before your other infusions In addition, as a preventive measure, you may be asked to stay overnight in the hospital for observation after the first two infusions of the study drug. For other doses, you will be asked to remain in the study center for at least 2 hours after the end of the infusion.

There is a risk of tumor lysis syndrome due to tumor shrinkage. This complication is caused by the breakdown products of dying cells and includes elevated blood potassium, elevated blood phosphorus, elevated blood uric acid and elevated urine uric acid, low blood calcium, and consequent acute kidney failure.

In addition, immune-related side effects might be possible. These adverse events are caused by over activity of your body's immune system. 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 are foreign substances and attack them.

Examples of these side effects are listed below. In rare cases, immune-related side effects can be life-threatening or fatal.

Types of immune-related side effects:

- pneumonitis (inflammatory disease of the lung): 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)
- hepatitis (inflammation of the liver). 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 normal
- thrombocytopenia (decrease of the blood platelets)
- uveitis (inflammation in the eyes)
- diabetes mellitus (high blood sugar levels)
- adrenal insufficiency: inability of the adrenal glands (triangle-shaped glands located on top of the kidneys) to produce a normal quantity of hormones. It 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 (inflammatory disease of muscles characterized by pain and tenderness)
- colitis (inflammatory disease of the large intestine). 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 (marked inflammation and damage to the heart)
- 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.
- Hypopituitarism (problems with the pituitary gland). 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 pancreas)
- 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

Risks of study research procedures

Blood draws

Risks include temporary discomfort, pain, redness, bleeding, bruising, and swelling at the site where the needle is inserted, and/or very rarely inflammation/infection of the vein, which could require antibiotics. You may also experience dizziness, nausea, or rarely, fainting during blood taking. Please tell the study doctor if you do not feel well after having your blood drawn.

Electrocardiogram (ECG)

Some skin irritation can occur where the ECG/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.

Tumor biopsy

If your doctor determines it is safe, we will obtain a piece of your tumor (biopsy) using a needle with minimal risk to you. You will be given local anesthesia (numbing medicine) and a sedative prior to the biopsy. The biopsy will be taken through a needle put through the skin into your tumor. Depending upon the location of your tumor, a CT scan may be used to assist the biopsy. After the procedure the nurses will watch your blood pressure and other vital signs. Two biopsies are mandatory, and one is optional. These biopsies will be used for conducting research and making clinical decisions. If an attempt at biopsy is unsuccessful, you will still be eligible for treatment.

There may be some temporary pain or discomfort during the procedure and afterwards in the area where the tissue was removed. You may also experience some bruising around the biopsy site over the following days. In rare cases an infection or bleeding may occur. Your doctor will give you a separate surgical consent form for this hospital procedure.

Imaging/scans

CT and/or MRI scans are used to monitor your disease while you are in this study. You may receive a contrast agent as part of your CT scan or MRI. 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. Please ask the study doctor if you have questions about the risks of these scans. If done, MRI scans do not involve radiation risk. The scans that you will receive during this study are considered standard for your type of disease.

MRI scans cannot be done on people who have:

- a cardiac pacemaker,
- neural pacemaker,
- surgical metal clips in the brain or on blood vessels,
- cochlear implants,
- or foreign metal objects within the eye.

At the time of your MRI, you will be asked about these things.

What are the risks related to pregnancy?

If you are able to become 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 65 days 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 a study team member 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 (at least 125 days after the last dose of the study drug - restricted period for male participants). It is equally important that you do not donate sperm for the same time period. There may be unknown risks to a 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 study team as soon as possible. If you and your partner plan for your partner to become pregnant after the restricted period (male or female as applicable), 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 up to 7 CT scans of chest, abdomen and pelvis and up to 3 CT guided biopsies. The amount of radiation exposure you will receive from these procedures is equal to approximately 10.1 rem. A rem is a unit of absorbed radiation.

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." This study will expose you to more radiation than you get from everyday background radiation. No one knows for sure whether exposure to these low amounts of radiation is harmful to your body.

The CT scans that you get in this study will expose you to the roughly the same amount of radiation as 33.7 years 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 1.0 out of 100 (1.0%) and of getting a fatal cancer is 0.5 out of 100 (0.5%).

Psychological or Social Risks Associated with Return of Incidental or Secondary Findings

As part of the research study, it is possible that you could learn that you have genetic risks for another disease or disability. This may be upsetting and, depending on what you learn, might create a need to make challenging decisions about how to respond.

Although your genomic information is unique to you, you share some genomic similarities with your children, parents, brothers, sisters, and other blood relatives. Therefore, learning your

research results could mean something about your family members and might cause you or your family distress. Before joining the study, it may be beneficial to talk with your family members about whether and how they want you to share your results with them.

Privacy Risks Associated with Return of Incidental or Secondary Findings

Although your genetic information is unique to you, you do share some genetic information with your children, parents, brothers, sisters, and other blood relatives. Consequently, it may be possible that genetic information from them could be used to help identify you. Similarly, it may be possible that genetic information from you could be used to help identify them. Patterns of genetic variation also can be used by law enforcement agencies to identify a person or his/her blood relatives.

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.

However, the potential benefit to you might be shrinking of your tumor or decrease in your symptoms, such as pain, that are caused by the cancer. Because there is not much information about the drug's effect on your cancer, we do not know if you will benefit from taking part in this study.

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

In the future, other people might benefit from this study because what we learn in this study may eventually be used to treat others with your disease.

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.

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

When we are examining your DNA, it is possible that we could identify possible changes in other parts of your DNA that are not related to this research. These are known as "incidental medical findings".

These include:

- Changes in genes that are related to diseases other than cancer
- Changes in genes that are not known to cause any disease. These are known as normal variations.
- Changes in genes that are new and of uncertain clinical importance. This means that we do not know if they could cause or contribute to a disease or if they are normal variations.

Since the analyses that we perform in our laboratory are not nearly as sensitive as the tests that are performed in a laboratory that is certified to perform genetic testing, the genetic changes that we find may or may not be valid. Therefore, we do not plan to inform you of all of the genetic results of testing on your tissue and blood that is performed in our research lab. However, in the unlikely event that we discover a finding believed to be clinically important based on medical standards at the time we first analyze your results, we will contact you. This could be many years in the future. We will ask you to have an additional tube of blood drawn to verify the findings we have seen in our lab. If the results are verified, you will be re-contacted and offered a referral to a genetic healthcare provider to discuss the results.

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 M7824 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 30 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 EMD Serono 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 urothelial cancer, 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 that are similar to this study or in other unrelated areas. These researchers may be at NIH, other research centers and institutions, or commercial 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. Usually, 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 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.

Summary information about all of the participants included in this study (including you) is being placed in a database and will be available through open access. That means that researchers and non-researchers will be able to access summary information about all the participants included in the study, or summary information combined from multiple studies, without applying for permission. The risk of anyone identifying you with this information is very low.

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 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 someone may 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.

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 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 NIH and the research team for this study have developed a drug being used 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 M7824.

The NIH and the research team for this study are using M7824 developed by EMD Serono through a joint study with 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

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 EMD Serono, the pharmaceutical company who produces M7824

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 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.

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, Andrea B. Apolo, andrea.apolo@nih.gov, at 301-480-0536. 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 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: _____.