PRINCIPAL INVESTIGATOR: Udo Rudloff, MD, PhD.

STUDY TITLE: A Phase I/II Study of The Immune Checkpoint Inhibitor M7824 and the Immunocytokine M9241 in Combination with Stereotactic Body Radiation Therapy (SBRT) in Adults with Advanced Pancreas Cancer.

STUDY SITE: NIH Clinical Center

Cohort: Phase 1A - Affected patient

Consent Version: 11/24/2021

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.

You are being asked to take part in this study because you have pancreatic cancer and your doctor has found that you are not a candidate for curative surgery.

The purpose of this study is to find a safe combination dose of M7824, M9241 and radiation (SBRT) and to see if this dose will cause your tumors to shrink.

The study is divided into 3 parts. In phase 1A, we will try to find a safe dose combination for M7824 and M9241. In phase 1B, we will try to find a safe dose combination for M7824, M9241 and radiation (SBRT). In phase 2, we will determine if the dose found in phase 1B will cause your tumors to shrink. You will participate in phase 1A of the study and will not receive radiation.

The use of M7824 and M9241 in this study is considered investigational which means these drugs have not been approved by the U.S. Food and Drug Administration (FDA) to treat cancer. However, the FDA has given us permission to use these drugs in this study.

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

M9241 is designed to trigger your immune system to fight your cancer.

Although M7824 and M9241 have both been studied independently in clinical trials, there is no clinical data for the combination M7824 and M9241.

Radiation therapy is sometimes used with drugs to treat symptoms caused by the tumor. We also believe it helps prevent tumors from evading your immune system.

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: chemotherapy that is known as platinum-based (such as cisplatin) or taxane based (such as paclitaxel, abraxane or docetaxel are some possible treatments that you could receive. The treatment being given in this study and the side effects are different than if you were to receive standard care. For example: 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). These new drugs (M7824 and M9241), belong to a group of drugs called immune checkpoint inhibitors and although they may cause similar side effects, they have also been found to cause skin problems (such as rash), problems with the immune system, and bleeding.

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.

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

- First, we will perform tests to find out if you fit the study requirements. We will do standard blood tests and scans to test your health and see the status of your disease.
- You will have study treatment with just the combination of M7824 and M9241 (group 1A)).
- 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. It could also be given through a central catheter if you already have one installed.
- M9241 is an injection given under the skin. This is similar to receiving a vaccine shot and is given every four weeks.
- You will not generally need to stay in the hospital for this study.
- We will need to see you at the Clinical Center every 2 weeks while you are receiving study treatment. Study treatment will last for as long as you are tolerating and benefiting from the study drugs. Each visit should last no more than 8 hours. At your visits you will have clinical, laboratory and imaging tests to see how you are doing. We will ask you to complete questionnaires (if you read English) and collect required blood samples, tissue (if you have surgery while on study) and scans from you for both clinical and research purposes.
- We hope that during the study treatment your tumors shrink, and you become a candidate for curative surgery. In this case we will stop study treatment and you will have surgery at your home institution or with enrollment to another clinical trial here at the Clinical

Center. If your cancer is removed completely, you will not get any further study therapy. If your cancer is removed only partially, you can continue study therapy after you recover from the surgery.

- As described above and later in more detail in this consent form, you may have side effects if you take part in this study. Some can be mild or very serious, temporary, long-lasting, or permanent, and may include death. You will be seen regularly during the study. You will have clinical, laboratory, and imaging tests to see how you are doing and see how your disease is responding.
- It is possible that the low red blood cell counts and/or bleeding may be so severe that you require a blood transfusion.
- After the study treatment has ended, we would like to see you in the Clinical Center approximately one week and one month later to check on your health. After that we are planning to contact you by phone or e-mail to learn about your health status, and to see how you are doing, for the rest of your life or until the study is stopped. If you stop study treatment for reasons other than worsening of your disease, we will continue to invite you for imaging studies approximately every 12 weeks until your disease gets worse. You can have these studies done locally and send us the results.
- Some drugs and vaccines are not allowed during this study. Please, let you doctor know about all medicines you are taking or planning to take.

This study may benefit you by shrinking of your tumor or lessening of your symptoms, such as pain, that are caused by the cancer. Even if you do not benefit from this study, the results from our research will help others in the future.

You are free to stop taking part 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 treatments they would want to receive (such as blood transfusions). 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 is a research study. The purpose of this study is to find a safe combination dose of M7824, M9241 and radiation (SBRT) and see if this dose will cause your tumors to shrink.

The study is divided into 3 parts. In phase 1A, we will try to find a safe dose combination for M7824 and M9241. In phase 1B, we will try to find a safe dose combination for M7824, M9241 and radiation (SBRT). In phase 2, we will determine if the dose found in phase 1B will cause your tumors to shrink.

You will participate in phase 1A of the study and will not receive radiation.

We are asking you to join this research study because you have pancreatic cancer and your doctor has found that you are not a candidate for curative surgery.

The use of M7824 and M9241 in this study is considered investigational which means these drugs have not been approved by the U.S. Food and Drug Administration (FDA) to treat cancer. However, the FDA has given us permission to use these drugs in this study.

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

M9241 is designed to trigger your immune system to fight your cancer.

Radiation therapy is sometimes used with drugs to treat symptoms caused by the tumor and may also help prevent tumors from evading your immune system.

WHAT WILL HAPPEN DURING THE STUDY?

You will get study treatment in cycles (1 Cycle = 28 days).

You will get a treatment combination of M7824 + M9241.

M7824 will be given to you through an IV (intravenous catheter, a small plastic tube that is put into a vein, usually in your arm) once every 2 weeks (on days 1 and 15 of every cycle). You will have additional infusion on Day -14, that is, two weeks before the start of cycle 1.

M9241 is an injection given under the skin. This is similar to receiving a vaccine shot and will be done once every 4 weeks (on day 1 of every cycle).

If your doctor is convinced that you have unacceptable side effects caused by one of study treatment drugs, this drug will be stopped, and you may continue study treatment with the other drug if your study doctor finds that it is in your interest.

If you have serious side effects caused by the study treatment, treatment can be paused and restarted if you feel better and your doctor thinks it is in your best interest. The dose of M9241 may be reduced at that time.

Study treatment will continue until you have unacceptable side effects (both drugs), or you are no longer benefiting from the study therapy.

If during the study treatment your tumors shrink, and you become a candidate for curative surgery, we will stop study treatment, so you can have surgery. This surgery will be done at your home institution or with enrollment to another clinical trial here at the Clinical Center. If your cancer is removed completely, you will not get this study treatment anymore. If your cancer is removed only partially, you can continue this study treatment after you recover from the surgery. Before you continue study treatment, we will do standard clinical exams and tests to make sure you are still eligible for this study.

Study treatment and all study related procedures will be done during outpatient visits without planned hospitalization.

Some drugs and vaccines are not allowed during this study.

Please, let your study doctor know about all medicines you are taking or planning to take. **Do not start any new drugs, herbal remedies, or dietary supplements before talking to your study doctor.**

Before you begin the study

Before you begin this study, you will need to have standard clinical exams and tests to make sure you are eligible for this study. The exams and tests are part of regular cancer care. These tests will be done under a separate protocol.

You will also be asked to provide documentation to confirm your diagnosis. If documentation is not available, we will perform a biopsy (collect a sample of your tumor) to confirm your diagnosis.

If study treatment does not start within 28 days after enrollment to this study, some tests may need to be repeated.

During the study

Ongoing procedures before study treatment and on the first day of each cycle:

- Physical examination, including weight, vital signs.
- Review of your medications and your ability to perform your normal activities.
- Discussion of any symptoms you might be having
- Routine blood tests to find out if you are anemic, have low blood counts, and if your liver, kidneys, thyroid, clotting system and other organs are working well
- Pregnancy test if you are a woman who can have children
- Blood test for tumor markers
- Routine urine test

Additional Procedures:

- Physical examination, including weight, vital signs, discussion of your symptoms and assessment of your ability to perform your normal activities on day 15 of each cycle
- Electrocardiogram (EKG – a record of your heartbeat) to evaluate your heart before study treatment, on days 1 and 15 of cycle 1.

- Routine blood tests to find out if you are anemic, have low blood counts, and if your liver, kidneys, and other organs are working well on Day 15 of each cycle .

  Imaging assessments - a CT scans (a series of x-ray images taken of parts of your body) of chest, abdomen and pelvis before study treatment, approximately 10 weeks after beginning of the study treatment and every 8 weeks after that.

When you are finished taking the drugs (study treatment)

Approximately 7 and 28 days after you have finished taking the study drug, you will be asked to return to the Clinical Center for safety follow up visits. At these visits, you will be asked questions about your health, get a physical exam and undergo blood tests for clinical and research purposes. An EKG will also be performed.

If you have been taken off study treatment for reasons other than worsening of your disease, you will continue to have imaging studies approximately every 12 weeks until worsening of your disease. You can have these studies at home institution and send us results.

If you are unable to return for these visits, we will obtain the information from you by telephone or e-mail.

Once you stop coming to Clinical Center for safety visits and your scans, we will call or e-mail you every 3 months for first year and every 6 months after that to ask you about your general well-being.

Blood draws

You will have blood drawn during the study. These samples will be drawn to monitor your health during the study participation at every visit to the Clinical Center (about 3 tablespoons at each visit) and for research purposes, as described in the next sections (about 2 tablespoons at visits to occur once a month). If you participate in Group 1A, you will have additional blood drawn (less than 1 tablespoon) before treatment, on days -14 and day 15 of cycle 1 as explained in the next section.

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 and perform tests for purposes of research only.

The samples will be used to check drugs levels and stability in the blood and to look at the effects of the therapy on the immune system and the tumor:

- Blood samples to study:
  - **(**Drug levels in your blood on days -14 and day 1 of cycle 1 collected before study treatment and approximately 1 hour after study treatment, and on day 15 of cycle 1 before study treatment.
  - Stability of drugs and how immune system is affected by the study treatment before treatment and on day 1 of every cycle.

- We will ask you to provide samples of your tumors from previous surgeries or biopsies if available and from surgery while on study if you have the surgery. Samples will be used to study your tumor genes and effects of therapy on the tumor.

  Tumor and blood samples collected for research purposes on this study 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 "DNA sequencing." This is where we will do special tests in the lab to look at the sequence, or order, of how your DNA or RNA are 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 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.

  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.

- Magnetic Resonance Imaging (MRI) to evaluate how well the drugs circulate in your tumor before start of study treatment, on day 1 of cycles 1 and 3.

You will be asked to complete questionnaires to determine you general well-being and function - before start of study treatment on cycles 2, 4, every 12 weeks after that. It will take you about 20 minutes and will only be done if you can complete the surveys in English.

HOW LONG WILL THE STUDY TAKE?

You will come to the NIH Clinical Center to get study treatment and check status of your health every two weeks until your disease gets worse or you have unacceptable side effects at which time we will stop study treatment.

Visits will range from 4-8 hours in length.

After stopping study treatment, we would like to see you in the NIH Clinical Center one week and one month later and follow you after that for the rest of your life by telephone or e-mail.

If you stop study treatment for reasons other than worsening of your disease, we would like to invite you for imaging studies approximately every 12 weeks until worsening of your disease.

HOW MANY PEOPLE WILL PARTICIPATE IN THIS STUDY?

We plan to have up to 15 people take part in the first phase of this study.

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

The drug 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.

Here are important points about side effects:

- The study doctors do not know who will or will not have side effects.
- Some side effects may go away soon, some may last longer.
- Some side effects may be serious and may even result in death.

Here are important points about how you and the study doctor can make side effects less of a problem:

- Tell the study doctor if you notice or feel anything different so they can see if you are having a side effect.
- The study doctor may be able to treat some side effects.
- The study doctor may adjust the study drugs to try to reduce side effects.

M7824

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 gums, nose, ears, eyes, vagina, breast, blood in the urine, stool, or bleeding in the internal organs or skull, coughing up or vomiting blood. Bleeding may also occur at sites of disease (tumor sites). 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 tiredness and shortness of breath. May require a 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 study 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.

In addition, immune-related side effects are possible. These side effects are caused by over activity of your body’s immune system. The immune system normally works to protect you from things

that are harmful such as infections, foreign substances, and sometimes from cancer. If the immune system is overactive, it can attack normal parts of the body because it mistakenly recognizes them as foreign/harmful.

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:

- 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 normal
- Thrombocytopenia (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 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.

M9241

M9241 is in the early stages of development and, as such, the potential side effects are not completely known. A recent study of 58 patients treated at the NCI with M9241 alone showed that the majority of patients experience some side effects (81.4%) but very few patients experience serious study treatment-related side effects (3.4%).

The following drug-related side effects have been observed in **more than 10%** of the 58 participants treated with M9241:

- decreased white blood cells (including lymphocytes and neutrophils) which increases the risk of infection
- fever
- decreased liver function, as seen by increased liver enzymes in the blood
- increased blood sugar
- anemia caused by decreased number of red blood cells
- flu-like symptoms
- increased alkaline phosphatase (an enzyme found in the blood)
- decreased platelets, which increases the risk of bleeding
- tiredness
- decreased albumin levels in the blood
- decreased phosphate levels in the blood

If you suffer any of these side effects (or any others not listed) or you think you are experiencing a side effect during this study, you must tell your study doctor immediately

Risks from Blood Collection

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

Risks from CT scans

If contrast dye is used, there is a risk for allergic reaction to the dye. If you are allergic to or sensitive to medications, contrast dye, iodine, or shellfish, please notify your study doctor. If you have had kidney failure or other kidney problems in the past, please notify your study doctor.

Risk from Electrocardiogram

You may experience some minor skin irritation from the electrodes.

Risks of urine collection

There are no risks of urine collection.

Risks from Questionnaires

Questionnaires may contain questions that are sensitive in nature. You may only answer questions that you are comfortable with.

Risks from 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.

It is not known if MRI 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. The scan will not be done if the pregnancy test is positive.

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.

During part of the MRI you will receive gadolinium, a contrast agent, through an intravenous (iv) catheter. It will be done for both research and medical purposes.

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" which 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 not normal or if you received gadolinium within the previous month.

Most of the gadolinium contrast leaves the body in the urine. However, the FDA recently 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 than others. In this study, we will use the gadolinium contrast drugs that are less likely to remain.

Please tell your research team if you have had any MRI scans in the past 12 months. 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 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 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 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 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?

You will be exposed to radiation from up to 7 CT scans used to plan your treatment and measure your progress. The amount of radiation exposure you will receive from these procedures is equal to approximately 7.7 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 26 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 0.8 out of 100 (0.8%) and of getting a fatal cancer is 0.4 out of 100 (0.4%).

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.

Privacy Risks Associated with Genetic Testing

It may be possible that genetic information from you could be used by law enforcement agencies or other entities to identify you or your blood relatives.

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.

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. However, the Genetic Information Nondiscrimination Act (GINA) is a federal law that makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. However, GINA does not prevent discrimination from 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 genetic condition or disease.

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 include shrinking of your tumor or lessening of your symptoms, such as pain, that are caused by the cancer.

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 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.

EARLY WITHDRAWAL FROM THE STUDY

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

- if your disease worsens or comes back during study treatment
- if you become pregnant
- if you have side effects from the study treatment that your doctor thinks are too severe
- if you need treatment that is not allowed on this study
- if study drugs become unavailable
- if new information shows that another treatment would be better for you
- if the study is stopped for any reason

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

After the therapy is stopped, we would like to see you for a safety visit approximately one week and one month after stopping therapy.

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.

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 pancreatic 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 similar to this research 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. 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.

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 your 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 NIH and the research team for this study are using M7824 and M9241 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 of National Cancer Institute.
- Qualified representatives from EMD Serono, the pharmaceutical company who provides M7824 and M9241.

When results of an NIH research study are reported in medical journals or at scientific meetings, the people who take part are not named and identified. In most cases, the NIH will not release any information about your research involvement without your written permission. However, if you sign a release of information form, for example, for an insurance company, the NIH will give the

insurance company information from your medical record. This information might affect (either favorably or unfavorably) the willingness of the insurance company to sell you insurance.

If we share your specimens or data with other researchers, in most circumstances we will remove your identifiers before sharing your specimens or data. You should be aware that there is a slight possibility that someone could figure out the information is about you.

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, Udo Rudloff, MD, PhD, rudloffu@mail.nih.gov, 240-760-6238. 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: _____.