PRINCIPAL INVESTIGATOR: Anish Thomas, M.D

STUDY TITLE: Safety Run-In and Phase II Trial of M7824 and Topotecan or Temozolomide in Relapsed Small Cell Cancers

STUDY SITE: NIH Clinical Center (CC)

Cohort:	Affected Patient
Consent Version:	01/11/2024

WHO DO YOU CONTACT ABOUT THIS STUDY?

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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). 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. Taking part in research at the NIH is your choice.

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?

Small cell lung cancer (SCLC) is an aggressive cancer with poor outcomes. Patients with SCLC tend to be very responsive to chemotherapy in the beginning but then become resistant to treatment after a few months. There have been different strategies used over the years to treat SCLC without successful breakthroughs; therefore, there is a need for new treatment approaches.

Extrapulmonary small cell cancers are not common cancers and there are no standard treatment for this disease. It has been discovered that patients with extrapulmonary small cell cancers may respond to similar treatment to that of patients with SCLC.

Chemotherapy drugs currently used to treat SCLC work by altering DNA of cancer cells; however, they do not destroy all cancers cells due to the ability of cancer cells to repair their damaged DNA.

In this study we would like to test topotecan and temozolomide in combination with a drug called M7824. Topotecan is approved by the FDA for use in small cell lung cancer, ovarian cancer and in cancers of the cervix. Temozolomide is approved by the FDA to treat brain cancers, but has shown activity in SCLC in small studies. M7824 is an investigational immunotherapy agent designed to block the ability of cancer cells to avoid being destroyed by immune system. Investigational means that it has not been approved by the US Food and Drug Administration. The aim of this investigational drug is to control tumor growth by helping the immune system to fight the tumor. We think that increased DNA damage to cancer cells caused by topotecan and temozolomide will complement the anti-tumor activity of M7824, in recurrent SCLC.

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.

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.

Approximately the first 6 participants enrolled in the study will receive M7824 alone to test for safety in the first part of the study. We will then test how effective the combinations of M7824 and topotecan or M7824 and temozolomide are in treating SCLC. For a group of 10 participants with extrapulmonary small cell cancer, we will also test how effective the combination of M7824 and temozolomide is in treating this type of cancer.

We will start with one dose of M7824 in this group of participants, but the dose may be lowered in later participants if we find it causes too many side effects. The dose that does not cause too many side effects will be considered a safe dose. We will test the safe dose in the next group of participants to see if it's effective.

WHY ARE YOU BEING ASKED TO TAKE PART IN THIS STUDY?

You have been asked to take part in this study because you have been diagnosed with Small Cell Lung Cancer (SCLC) or extrapulmonary small cell cancer, and your disease has not responded to prior treatment.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

Up to 80 people will take part in this study.

DESCRIPTION OF RESEARCH STUDY

WHAT WILL HAPPEN IF YOU TAKE PART IN THIS RESEARCH STUDY?

Before you begin the study

Before you begin this study, you will have several exams and tests to make sure you are eligible for this study. The following tests may be performed on this study, another NIH protocol or records may be collected from your outside provider:

- Medical history and physical examination to determine your current health status.
- Blood tests to assess how your organs are functioning (about a tablespoon of blood will be collected).
- As part of this study, we will test you for infection with the human immunodeficiency virus (HIV), the virus that causes AIDS, and hepatitis B and C (about a tablespoon of blood will be collected for these tests). If you are infected with HIV and you are receiving treatment, you will be able to be in this study. If you have hepatitis B, hepatitis C, or you are not receiving treatment for HIV, you will not be part of the study. We will tell you what the results mean, how to find care, how to avoid infecting others, how we report these infections, and the importance of informing your partners who are at possible risk because of your viral infection.
- Electrocardiogram (EKG) – An electrocardiogram (ECG) is a test that looks at electrical activity of your heart. You will need to lie still for about 5 minutes. We will place electrodes on your chest, arms, and legs. Electrodes are small stickers that are attached to wires that go to the machine. The signals are recorded by the machine. If you have a lot of hair on your chest, it may hurt a little bit to remove the stickers.
- CT scan – The CT scanner is a donut-shaped machine that uses x-rays to make computer pictures of the inside of your body. During the procedure, you will need to lie still on a table inside the CT machine. The table will move you in and out of the machine during the scan, and you will be told to hold your breath.
- PET scan (may not need to be performed if your study doctor determines the CT to be sufficient) – The PET scanner is a donut-shaped machine that uses x-rays combined with a dose of a radioactive material (tracer) to make computer pictures showing the inside of your body.
- We will confirm your diagnosis by reviewing records from past biopsies.
- Pregnancy Test - If you are a woman who can become pregnant, you will have a pregnancy test done through a urine or blood test (about a teaspoon of blood may be drawn).

During the study

The first group (Arm A) will consist of about 10 participants who will enroll and receive M7824 alone. Two doses of M7824 will be evaluated. You will receive M7824 through a tube inserted in your vein for approximately 1 or 2 hours on day 1 of a 21-day cycle depending on the dose received. You will continue this therapy as long as the disease is responding to treatment. If your disease worsens, you may be assigned to receive M7824 in combination with temozolomide. Any time you take temozolomide, you may be given drugs to help with infections that have been associated with temozolomide. If there are no slots available in the combination arms, we will discuss other potential clinical trials with you.

After Arm A has completed, the next participants will be assigned to receive M7824 in combination with temozolomide (Arm C). If enrollment of SCLC participants in Arm C is complete, then participants will be assigned to receive M7824 in combination with topotecan (Arm B). A small number of participants with extrapulmonary small cell cancer will also be enrolled in Arm C.

If you have been assigned to Arm B, you will receive M7824 in your vein for approximately 2 hours on day 1. You will receive topotecan in your vein for approximately 30 minutes on day 1 within 15-30 minutes after you finished infusion of M7824. You will continue receiving topotecan every day for an additional 4 days and a total of 5 days including day 1. Each cycle of therapy will be 21 days.

If you have been assigned to Arm C, you will receive M7824 in your vein for approximately 1 hour on days 1 and 15. You will take temozolomide by mouth within 15-30 minutes after you finished infusion of M7824 on day 1 and continue taking temozolomide once daily for a total of 5 days. You will be given a pill diary at the beginning of each cycle to fill out and bring back to the study nurse at the end of the cycle. You will take temozolomide on an empty stomach with a glass of water. Capsules should be swallowed whole and should not be opened or chewed. Each cycle of therapy will be 28 days.

If you are receiving M7824 plus one of the chemotherapy agents (topotecan or temozolomide), treatment will be continued until your disease progresses. If you are in arm B or C and cannot tolerate the chemotherapy agent, M7824 alone may be continued until your disease progresses if your study doctor finds that you are benefiting from therapy. This would not apply for arm A participants receiving M7824 and temozolomide who already had their disease worsen on M7824 alone.

For the safety run-in portion of the study, participants will be enrolled into each combination group and will receive treatment at a pre-planned dose. Once each combination group enrolls at least 6 participants, enrollment will be paused to assess the safety of the combinations. For each drug combination, if the dose given during the safety lead-in is considered safe, the remaining participants will receive the same dose. If too many side effects occur, remaining participants will receive a lower dose. If there are too many side effects at the reduced dose, then no more participants will be enrolled for that combination.

There will be a second pause in enrollment after 10 participated have received each combination to find out whether the combinations are helping to shrink your tumor (an efficacy assessment). Enrollment will continue after this point only if the combination in question appears to have some effect on tumor size. It is possible that none, one or both of the combinations will move beyond the efficacy assessment.

Research Studies

An important part of the research is to determine how your body and tumor respond to the combination of drugs. To understand this, we will collect your blood, tumor, and hair follicles at different time points. Biopsies will be optional. If you agree to have the biopsies, these will be performed before you start treatment and during cycle one day 15 or cycle two day 1 depending on the arm you are assigned to. You will be asked to sign a separate consent for the biopsy at the time of the procedure.

You may receive conscious sedation before undergoing a biopsy. Conscious sedation is usually given to help someone relax and minimize discomfort. It can be given as a pill, a shot, an IV (intravenous catheter, a small plastic tube that is put into a vein, usually in your arm) or even inhaled. You may have to wait up to an hour to start feel the effects depending on how it is given. Once it takes effect, you will be mostly awake, though relaxed or drowsy. You will be monitored throughout the procedure.

We will be using the biopsies and blood samples to look at the genes (pieces of DNA) that are present in tumor cells and in blood cells. We will be using the hair follicles to look for any damage in your DNA that might lead to inflammation which might cause cancer. This information may help us understand why some patients respond to certain treatments better than the others. In the course of examining your DNA, it is possible that we could identify possible changes in genes that are not the target of our investigation, but which are associated with diseases. These are called incidental or secondary findings.

Some of your samples may be tested in a laboratory that is certified to perform genetic testing. If this happens, we will offer to share the results for these tests. Some of the analyses will be performed in our laboratory and 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. Changes that we observe unrelated to our research may or may not be valid. Therefore, we do not plan to inform you of the results of testing on your specimens that is performed in our research lab. However, in the unlikely event that we discover a finding that is 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 provide a sample to verify the findings we have seen in our lab. If the results are verified, you will be re-contacted and referred to a genetic healthcare provider to discuss the results.

Please see the section discussing the risks that you might experience other than the drug side effects for the implications of receiving genetic information.

We will also collect your blood in order to see how quickly study medications are processed in your blood. These are called pharmacokinetic studies. These studies may require hospitalization. The timelines of when we will collect blood for pharmacokinetic studies are shown below and in the study chart.

Arm A (M7824 only): We will collect blood samples before and after the infusion when you receive dose 1 as well as 24 hours after the infusion; before and after dose 3; and before the infusion when you receive doses 2 and 6 of M7824 and at the end of treatment.

Arm B (M7824 and topotecan): If you are assigned to this arm, we will also sample your blood on day 1 of the first cycle to test the levels of topotecan. Blood will be collected before the chemotherapy infusion and periodically (6 -7 times) after the chemotherapy infusion for up to 24 hours. Additional blood collection will be done 3 days and 5 days after the infusion as well.

Arm C (M7824 and temozolomide): If you are assigned to this arm, we will also sample your blood on day 1 of the first cycle to test the levels of temozolomide. Blood will be collected before the chemotherapy infusion and periodically (6 - 7 times) after the chemotherapy infusion for up to 24 hours.

When you are finished taking the drugs (treatment)

In the case that you have to stop receiving treatment, you will have a clinic visit approximately 4 weeks after you discontinue taking the study drugs, in which the health care provider will perform a physical exam and blood will be drawn.

STUDY CHART

Day	What to do and what will happen to you
Before starting	The research team's health care provider will go over your medical history and will perform a physical exam. Laboratory tests will be performed to measure organ functions (up to 2 tablespoons). An electrocardiogram and CT scan will be performed. A PET scan may be added if the CT scan is not sufficient. Blood test to measure troponin (an enzyme produced by a heart when its damaged) levels will be performed. About a teaspoon of blood may be collected. Blood test for certain viruses will be performed. About a tablespoon of blood may be collected. We will perform a neurological examination to measure the strength of your muscles. You will have a pregnancy test if you are a woman who can become pregnant. If tested by blood, about a teaspoon may be collected.

Cycle 1

Day 1	The research team's health care provider will perform a physical exam. [1, 5] Laboratory tests will be performed to measure organ functions (up to 2 tablespoons). Blood samples will be collected for research purposes (about 3 and a half tablespoons). [2] Blood will be collected to measure levels of drug (pharmacokinetics - about a tablespoon of blood at each timepoint). Hair follicles will be collected for research purposes. We will perform a neurological examination to measure the strength of your muscles. You will receive M7824 alone or in combination with topotecan or temozolomide.

	An optional tumor biopsy will be performed.
Day 2 **(24 hours after infusion)**	Blood will be collected to measure levels of drug (pharmacokinetics - about a tablespoon of blood). Hair follicles will be collected for research purposes.
Day 3 **(48 hours after infusion)**	Blood will be collected to measure levels of drug (pharmacokinetics – about a tablespoon of blood) if you are receiving M7824 in combination with topotecan.
Day 5 **(96 hours after infusion)**	Blood will be collected to measure levels of drug (pharmacokinetics - about half a tablespoon of blood) if you are receiving M7824 in combination with topotecan.
Day 15 [3] **(Arm C only)**	The research team's health care provider will perform a physical exam. Laboratory tests will be performed to measure organ function (up to 2 tablespoons). Blood samples will be collected for research purposes (about 3 tablespoons). [2] Blood will be collected to measure levels of drug (pharmacokinetics – about a tablespoon of blood). You will receive M7824. An optional tumor biopsy will be performed. You will have a pregnancy test if you are a woman who can become pregnant. If tested by blood, about a teaspoon may be collected. You will receive M7824.

Cycle 2

Day 1	The research team's health care provider will perform a physical exam. Laboratory tests will be performed to measure organ functions (up to 2 tablespoons). Blood samples will be collected for research purposes (about 3 tablespoons). [2, 4] Blood will be collected to measure levels of drug (pharmacokinetics - about a tablespoon of blood). Hair follicles will be collected for research purposes (arms A and B). We will perform a neurological examination to measure the strength of your muscles. You will receive M7824 with or without topotecan or temozolomide depending on your treatment assignment.

	An optional tumor biopsy will be performed if you are in the group to receive M7824 alone or in combination with topotecan. You will have a pregnancy test if you are a woman who can become pregnant.
Day 15 [3] **(Arm C)**	The research team's health care provider will perform a physical exam. Laboratory tests will be performed to measure organ functions (up to 2 tablespoons). Hair follicles will be collected for research purposes. You will have a pregnancy test if you are a woman who can become pregnant. If tested by blood, about a teaspoon may be collected. You will receive M7824.

Cycle 3 and beyond

Day 1	The research team's health care provider will perform a physical exam. Laboratory tests will be performed to measure organ functions (up to 2 tablespoons). CT scan will be performed either every 6 weeks or 8 weeks until disease progression depending on the arm you are enrolled in. A PET scan may be added if the CT scan is not sufficient. Blood samples will be collected for research purposes (about 3 tablespoons). We will perform a neurological examination to measure the strength of your muscles. You will receive M7824 with or without topotecan or temozolomide depending on your treatment assignment. You will have a pregnancy test if you are a woman who can become pregnant. If tested by blood, about a teaspoon may be collected.
Day 15 [3] **(Arm C)**	The research team's health care provider will perform a physical exam. Laboratory tests will be performed to measure organ functions (up to 2 tablespoons). You will have a pregnancy test if you are a woman who can become pregnant. If tested by blood, about a teaspoon may be collected. You will receive M7824.

Off Treatment

	The research team's health care provider will perform a physical exam.

	Laboratory tests will be performed to measure organ functions (up to 2 tablespoons). CT scan will be performed either every 6 weeks or 8 weeks until disease progression depending on the arm you are enrolled in. A PET scan may be added if the CT scan is not sufficient. [2] Blood samples will be collected for research purposes (about 3 tablespoons). We will perform a neurological examination to measure the strength of your muscles.

[1] Some of the tests may not need to be repeated again if they were performed close to the start of your treatment.

[2] You will have to be admitted to a hospital overnight on this day in order to collect blood for pharmacokinetic studies (if performed on that day).

[3] This visit will take place only if you are in a group to receive M7824 with temozolomide (Arm C).

[4] Blood for pharmacokinetic studies will be collected for the last time at the time you will receive the sixth dose of M7824 which will fall on cycle 3 day 15, if you are in Arm C, or cycle 6 day 1 if you are in Arm A or Arm B.

[5] If you are enrolled on the combination treatment of M7824 and temozolomide, you will have additional laboratory tests to measure organ functions on days 7 and 21. Since these are not the days you would come in for treatment, these labs can be performed by your local doctor and results faxed to us. Note: At each study visit, you will be able to report any side effects that you have experienced to the research team. You will also need to bring the completed pill diary.

BIRTH CONTROL

If you are able to become pregnant, we will ask you to have a pregnancy test before starting this study. You must use effective birth control methods and try not to become pregnant during study treatment, and for 6 months after you finish study treatment. 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 while you are in the study. If you think or know you have become pregnant while participating in this research study, please contact the study team as soon as possible. If you plan to become pregnant in the future, please discuss with the study team how long you need to wait before becoming pregnant after completing the study.

If you are a sexually active person with a partner able to become pregnant, it is important that your partner not become pregnant during study treatment, and for 3 months after you finish study treatment. 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. You should not donate sperm for the duration of the study and for 3 months after your last dose of study drug. If you think your partner has become pregnant during your participation in this study, please contact the study team as soon as possible. If you and your partner plan for your partner to become pregnant after your participation in this study, please discuss this with the study team.

RISKS OR DISCOMFORTS OF PARTICIPATION

From 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. 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 have 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 overactivity 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.
- Abnormal contraction of the intestinal muscles which can lead to severe constipation, nausea or vomiting. You may also experience loss of appetite and weight loss.

Embryofetal toxicity

Based on how the study drug works, there is also a risk of embryofetal toxicity (risks to your unborn baby). Therefore, every effort should be made not to become pregnant or father a child while on treatment and for 120 days following the end of treatment.

From Topotecan

Likely, some may be serious (experienced by more than 20% of persons taking the drug)

- Anemia which may require a blood transfusion
- Low white blood cell counts
- Constipation, diarrhea, nausea, vomiting
- Fever
- Pain
- Bruising, bleeding
- Infection, especially when white blood cell count is low
- Tiredness
- Shortness of breath

Less likely, some may be serious (experienced by between 3 and up to 20% of persons taking the drug)

- Sores in mouth which may cause difficulty swallowing
- Headache
- Cough
- Scarring of the lungs

Rare but Serious (experienced by 3% of fewer of persons taking the drug)

- Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat
- Low white blood cell counts which may result in life-threatening infections

Note: Some of the side effects associated with these drugs could potentially lead to death.

From Temozolomide

Most common (seen in 20 or more out of 100 people taking temozolomide):

- Fatigue
- Swelling
- Fever
- Dizziness
- Hair loss
- Rash
- Nausea or vomiting
- Constipation or diarrhea
- Loss of appetite
- Muscle weakness, paralysis, or difficulty walking
- Trouble with memory
- Difficulty sleeping

Less Likely (seen in 4-20 out of 100 people taking temozolomide):

- Headache
- Seizure
- Infection, especially when white blood cell count is low
- Depression
- Anxiety
- Mouth sores
- Weight gain
- Cough
- Blurry vision
- Shortness of breath
- Anemia (low red blood cell count) which may cause tiredness
- Thrombocytopenia (low platelet count)
- Bruising and/or bleeding

- Damage to the bone marrow (which is not reversible) and may cause infection, bleeding, or require blood transfusions

Rare but Serious (seen in 3 or fewer out of 100 people taking temozolomide)

- Severe rash, including skin rash with blisters; can involve inside of the mouth and other parts of the body
- Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, and/or swelling of the face or throat
- Cancer of bone marrow caused by chemotherapy
- Interstitial lung disease (lung injury) which can cause respiratory failure
- Numbness or tingling of fingers or toes
- Liver damage which may cause yellowing of eyes and skin, swelling, and may result in liver failure.
- Abnormal contraction of the intestinal muscles which can lead to severe constipation, nausea or vomiting. You may also experience loss of appetite and weight loss.
- A new cancer including leukemia resulting from treatment.
- Damage to the lungs caused by an infection from fungus.

Risks you might experience other than the drug side effects

Radiation

During your participation in this research study, you will be exposed to radiation from up to 10 CT scans, up to 10 PET scans and 2 CT guided biopsies. The amount of radiation exposure you will receive from these procedures is equal to approximately 21.6 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 and PET scans that you get in this study will expose you to roughly the same amount of radiation as 72 years’ worth of background radiation. Being exposed to too much radiation can cause harmful side effects such as an increase in the risk of cancer. The risk depends on how much radiation you are exposed to. Please be aware that about 40 out of 100 people (40%) will get cancer during their lifetime, and 20 out of 100 (20%) will die from cancer. The risk of getting cancer from the radiation exposure in this study is 2.2 out of 100 (2.2%) and of getting a fatal cancer is 1.1 out of 100 (1.1%).

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.

CT contrast risks

Itching, hives or headaches are possible risks associated with contrast agents that may be used during CT imaging. Symptoms of a more serious allergic reaction include shortness of breath and swelling of the throat or other parts of the body. Very rarely, the contrast agents used in CT can cause kidney problems for certain participants, such as those with impaired kidney function.

Blood Draws

Risks associated with blood draw, which include pain and bruising, lightheadedness, and rarely, fainting

Hair Follicle Collection

The risk associated with hair follicle collection is pain.

Risks from Biopsy

This procedure usually causes only brief discomfort at the site from which the biopsy is taken. Risks of biopsy may include bleeding, injury to internal organs, and infection. Rarely, these complications from biopsy could result in hospitalization and require additional medical care. Risks of sedation will be described at the time of procedure.

There is a possibility that conscious sedation may be used for the procedure. The common side effects of conscious sedation include drowsiness, delayed reflexes, hypotension, headache, and nausea. These are generally mild and last no more than a few hours.

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. 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.

POTENTIAL BENEFITS OF PARTICIPATION

Are there benefits to taking part in this study?

The aim of this study is to see if this experimental treatment will cause your tumors to shrink. We do not know if you will receive personal, medical benefit from taking part in this study. These potential benefits could include shrinking of your tumor or lessening of 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, although the knowledge gained from this study may help others in the future who have cancer.

ALTERNATIVE APPROACHES OR TREATMENTS

WHAT OTHER CHOICES DO I HAVE IF I DO NOT TAKE PART IN THIS STUDY?

Instead of being in this study, you have these options:

- Getting treatment or care for your cancer without being in a study
- Taking part in another study
- Getting comfort care, also called palliative care. This type of care helps reduce pain, tiredness, appetite problems and other problems caused by the cancer. It does not treat the cancer directly. Instead, it tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.

Please talk to your doctor about these and other options.

STOPPING THERAPY

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

- if he/she believes that it is in your best interest
- if your disease comes back during treatment
- if you have side effects from the treatment that your doctor thinks are too severe
- if new information shows that another treatment would be better for you

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

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

CONFLICT OF INTEREST

The National Institutes of Health (NIH) reviews NIH staff researchers at least yearly for conflicts of interest. This process is detailed in a 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 but they do not need to report their personal finances to the NIH.

The National Institutes of Health and the research team for this study are using a drug (M7824) developed by EMD Serono through a joint study with your researchers and the company. The company also provides financial support for this study.

USE OF SPECIMENS AND DATA FOR FUTURE RESEARCH

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

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

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

Genomic Data Sharing

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.

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. Someone will work with you to provide 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.

CLINICAL TRIAL REGISTRATION AND RESULTS REPORTING

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

CONFIDENTIALITY PROTECTIONS PROVIDED IN THIS STUDY

Will your medical information be kept private?

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

- The NIH and other government agencies, like the Food and Drug Administration (FDA), which are involved in keeping research safe for people.
- National Institutes of Health Intramural Institutional Review Board
- Center for Cancer Research, NCI or their agent(s)
- Qualified representatives from EMD Serono, the pharmaceutical company that 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 of this document on sharing of specimens and data, and as further outlined in the following sections.

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

Certificate of Confidentiality

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

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

The Certificate does not protect your information when it:

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

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

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

Privacy Act

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

POLICY REGARDING RESEARCH-RELATED INJURIES

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

PROBLEMS OR QUESTIONS

If you have any problems or questions about this study, or about your rights as a research participant, or about any research-related injury, contact the Principal Investigator, Anish Thomas, M.D., anish.thomas@nih.gov, Telephone: 240-760-7343. 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: _____.