PRINCIPAL INVESTIGATOR: **Stanley Lipkowitz, M.D., Ph.D.**

STUDY TITLE: **Phase I/II Study of T-DM1 Alone Versus T-DM1 and Metronomic Temozolomide in Secondary Prevention of HER2-Positive Breast Cancer Brain Metastases Following Stereotactic Radiosurgery**

STUDY SITE: **NIH Clinical Center**

Cohort: All Study Participants

Consent Version: June 6, 2022

WHO DO YOU CONTACT ABOUT THIS STUDY?

Stanley Lipkowitz, M.D., Ph.D. by phone at 240-760-6129 or e-mail: lipkowis@navmed.nci.nih.gov

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.

The remaining document will now describe the research study in more detail. This information should be considered before you make your choice. Members of the study team will talk with you about the information in this document. Some people have personal, religious, or ethical beliefs that may limit the kinds of medical or research interventions in which they would want to participate. Take the time you need to ask any questions and discuss this study with NIH staff, and with your family, friends, and personal health care providers.

If the individual being asked to participate in this research study is not able to give consent 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?

The purpose of this study is to investigate whether Temozolomide given in combination with T-DM1decreases the chance of having new metastases in the brain.

T-DM1 (Kadcyla) is FDA approved standard treatment recommended for metastatic breast cancer.

Temozolomide is FDA approved drug used in the treatment of brain tumors and was demonstrated to prevent metastases to brain in mice.

This study has two parts: a phase I and a phase II. In phase I, we are going to evaluate the safety of using temozolomide in combination with T-DM1. Increasing doses of temozolomide will be given to participants in the study to find the highest dose of temozolomide that people can tolerate when given in combination with T-DM1. In phase II we will compare how well the recommended dose of temozolomide in combination with T-DM1 works compared to T-DM1 alone for prevention of new brain metastases.

Why are you being asked to take part in this study?

We are asking you to be in this study because you have a HER2-positive breast cancer that has spread to the brain already treated with stereotactic radiation or surgery.

How many people will take part in this study?

Up to 125 participants will take part in this study. Approximately 18 participants will be enrolled in the phase I part and approximately 98 participants will be enrolled in the phase II part.

Description of Research Study

Before you begin the study

Before you begin this study, you will need to have the following exams and tests to make sure you are eligible for this study. The exams and tests are part of regular cancer care. These tests may be done under this consent if you are screened under this protocol, and/or under a separate consent if you are screened under the screening protocol 01-C-0129.

- A review of any past or current medical conditions, medicines you are taking and cancer history.
- Physical examination, including height, weight, vital signs, and complete neurological exam.
- Echocardiogram (Echo – ultrasound of your heart) or MUGA (scan of your heart) to evaluate your heart.
- Review of your symptoms and your ability to perform your normal activities.
- Imaging Assessments – a computed tomographic scan (CT) that produces a picture of your body using a small amount of radiation and magnetic resonance imaging (MRI) that uses a magnetic field to produce an image of your body. These will be used to examine your chest, abdomen, pelvis, bones and brain.
- At screening, within 10 days prior to your enrollment on this study, you will have a maximum of 4 tablespoons of blood drawn for 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.
- At baseline, within 7 days prior to your first dose of study drug, you will have another ½ tablespoon of blood drawn for tests for HIV*, Hepatitis B and Hepatitis C. If your

screening tests were drawn within the same 7-day window, those will not have to be repeated at baseline. This would mean that not more than 4 ½ tablespoons will be drawn during this 7-day period. If those tests do need to be repeated, that would mean you will have a maximum of 7 ½ tablespoons of blood drawn within a 10-day period.

- Pregnancy serum or urine test if you are a woman who can have children.
- You will be asked to provide a pathologist's report from an accredited laboratory or sample of your tumor from a previous surgery so that we may confirm your diagnosis.

*As part of this study, we will test you for infection with the human immunodeficiency virus (HIV), the virus that causes AIDS. If you are infected with HIV you will not be able to participate in this study. We will tell you what the results mean, how to find care, how to avoid infecting others, how we report HIV infection, and the importance of informing your partners at possible risk because of your HIV infection.

During the study

Drug administration and schedule

Phase I

T-DM1 will be administered to you through an IV (intravenous catheter, a small plastic tube that is put into a vein, usually in your arm) on Day 1 of each cycle (1 cycle = 3 weeks) in the Clinical Center.

You also will start take orally temozolomide on Day 1 of each cycle and continue every day for the whole cycle. Please, do not eat anything for at least 2 hours before and 1 hour after temozolomide administration. Water is allowed during the fast period. You should swallow the capsules whole, in rapid succession, without chewing them with a full glass of water.

You will be given a Medication Diary to complete for each cycle. In the diary, you will be asked to record date, time and missing doses. Please bring the diary with you at every study visit.

You will continue treatment until your disease get worse.

Phase II

Phase II is a randomized study. You will be placed into one of two groups by chance (like flipping a coin). Group A will have treatment with T-DM1 only and Group B will have T-DM1 in combination with temozolomide treatment.

T-DM1 will be administered to you through an IV (intravenous catheter, a small plastic tube that is put into a vein, usually in your arm) on Day 1 of each cycle (1 cycle = 3 weeks) in Clinical Center.

If you are in group B, you also will start take orally temozolomide on Day 1 of each cycle and continue every day for the whole cycle. Please, do not eat anything for at least 2 hours before and 1 hour after temozolomide administration. Water is allowed during the fast period. You should swallow the capsules whole, in rapid succession, without chewing them with a full glass of water.

You will be given a Medication Diary to complete for each cycle. In the diary, you will be asked to record date, time and missing doses. Please bring the diary with you at every study visit.

You will continue treatment until your disease get worse.

Ongoing Procedures during each treatment cycle

While you are on the treatment, on the first day of every cycle you will have tests done:

- Physical exam and vital signs
- Review of your symptoms and your ability to perform your normal activities
- Routine blood tests to find out if you are anemic, have low blood counts, your blood is clotting normally, the status of your immune system and if your liver, thyroid, kidneys, and other organs are working well. A maximum of 4 tablespoons of blood will be drawn for this purpose each visit, every 21 days. If your baseline tests were done within 72 hours of your first dose of study medication, they will not need to be repeated on Day 1 of Cycle 1.
- Pregnancy test
- Routine urine tests

Additional Procedures:

- Every 12 weeks - Echocardiogram (Echo) to evaluate your heart
- Every 6 weeks - Imaging Assessments – a CT scan or MRI of chest, abdomen and pelvis and MRI of brain. After one year, imaging assessments will be done every 12 weeks.
- Before Cycle 1 and every 6 weeks you will be asked to complete questionnaires to determine if you have symptoms of depression, anxiety, and general well-being or function.

Some of these visits or procedures may be done with your local provider or with a telehealth (e.g. phone, videocall) visit with your study team if you are unable to return to the NIH.

Research tests

In addition to the tests that we will conduct to determine whether you are having side effects or if you are responding to the study therapy, we will also collect samples from you for purposes of research only. Some of the analyses will be done outside of the NIH, but your samples will not contain any information that can identify you. These studies include:

- Blood* samples to study the effects of therapy on your neuro and immune systems will be collected during every cycle.
- Blood samples will also be collected to study the movement of Temozolomide through your body, called pharmacokinetics. These samples will be collected at designated time points (pre dose, 1, 2, 3, 4, and 8 hours post dose of Temozolomide) in one day, one cycle

only, Phase I participants only. The total amount of blood to be collected for this purpose is less than 4 teaspoons.

- Lumbar puncture to obtain cerebrospinal fluid to study the effect of treatment on your neurological system. During a lumbar puncture, a needle is carefully inserted into the spinal canal low in the back and cerebrospinal fluid collected. You will be required to have two lumbar punctures: once before treatment and once after treatment, at Day 1 of Cycle 3. Additional three lumbar punctures to obtain cerebrospinal fluid may be performed during following cycles only if you agree, but these are not required.
- We will ask you to provider tumor samples if they are available from surgeries performed before or during the study, but you will not have any biopsies or resection performed just for research purposes.
- We will conduct genetic studies on the blood*, cerebrospinal fluid and tumor samples that you have provided in order to test genetic alterations related to your tumor.

Note: * A maximum of 3 tablespoons of blood will be drawn for the research studies each visit. Added to the maximum 4 tablespoons of blood drawn to monitor your side effects each visit, that equals a maximum of 7 tablespoons of blood to be drawn every 21 days. The additional 4 teaspoons of blood for the pharmacokinetics studies will be drawn one time only.

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

However, 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. 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 tissue and blood 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 that we first analyze your results, we will contact you. This could be many years in the future. We will ask you to have an additional tube of blood drawn to verify the findings we have seen in our lab. If the results are verified, you will be re-contacted and offered a referral to a genetic healthcare provider to discuss the results.

When you are finished taking the drugs (treatment)

You will be invited for follow up safety visit approximately 1 month after the last day you take the study drug. At this visit, you will have the following tests:

- Physical exam and vitals
- Review of your symptoms and your ability to perform your normal activities.
- Routine blood tests to find out if you are anemic, have low blood counts, your blood is clotting normally and if your liver, kidneys, and other organs are working well. A

maximum of 4 tablespoons of blood will be drawn at this visit, for a maximum of 4 tablespoons drawn within this 30-day period.

After that, we will contact you by telephone or email every three months to determine your health status and to find out about any new cancer treatments that you have begun.

Birth Control

If you are a woman who is breast feeding or pregnant, you may not take part in the study because we don't know how this medicine would affect your baby or your unborn child. If you are a woman who can become pregnant, you will need to practice an effective form of birth control before starting study treatment, during study treatment, and for 7 months after you finish study treatment. If you are the male partner of a woman who can become pregnant, you should practice an effective form of birth control and not donate sperm during the study and for 4 months after the last dose of study therapy. If you think that you or your partner is pregnant, you should tell your study doctor or nurse at once.

Effective forms of birth control include:

- Abstinence
- intrauterine device (IUD)
- hormonal [birth control pills, injections, or implants]
- tubal ligation
- vasectomy

Risks or Discomforts of Participation

If you choose to take part in this study, there is a risk that:

- You may lose time at work or home and spend more time in the hospital or doctor's office than usual
- You may be asked sensitive or private questions which you normally do not discuss.

There is also a risk that you could have side effects from the study drug.

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 a long time, or some may never go away.
- Some side effects may interfere with your ability to have children.

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 any symptoms.
- The study doctor may be able to treat some side effects.

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

What side effects or risks can I expect from being in this study?

Risk associated with Temozolomide:

Likely

- Constipation, nausea, vomiting, diarrhea
- Dizziness
- Muscle weakness, paralysis, difficulty walking
- Trouble with memory
- Tiredness
- Difficulty sleeping
- Hair loss

Less Likely

- Headache, seizure
- Infection, especially when white blood cell count is low
- Anemia which may cause tiredness
- Bruising, bleeding

Rare but Serious

- Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat
- Cancer of bone marrow caused by chemotherapy
- Damage to the bone marrow (irreversible) which may cause infection, bleeding, may require blood transfusions
- Rash
- Severe skin rash with blisters and can involve inside of mouth and other parts of the body

Risk associated with T-DM1:

Likely

- Constipation, nausea, vomiting
- Tiredness
- Headache
- Muscle and joint pain
- Bruising, bleeding
- Increased liver enzymes

Less Likely

- Dizziness
- Difficulty sleeping
- Rash
- Itchy skin
- Cough and shortness of breath
- High blood pressure
- Taste change

Rare but Serious

- Low potassium
- Peripheral neuropathy
- Liver failure

Risks from Blood collection:

Local pain, bruising, bleeding, blood clot formation, and, in rare instances, an infection might occur at the site where blood is drawn. There is also the possibility of dizziness or fainting while your blood is being drawn.

Risks from Echocardiograms:

An echocardiogram is a painless test using sound waves to take a picture of your heart. A jelly-like substance will be placed on your chest and the technician will put the ultrasound probe on your chest and record the picture. The technician may ask you to lay on your side during the test to get a better picture. During some pictures, they may put the probe on the upper part of your abdomen and push down firmly. This can be uncomfortable. The test takes about 30 minutes to

complete.

Other than the possibility of some mild discomfort during the test, there are no known risks to an echocardiogram.

Risks from MUGA scans:

A multiple-gated acquisition (MUGA) scan is an imaging test that looks at how much blood your heart pumps out with each contraction, which is called the ejection fraction.

In addition to the risks of radiation exposure, which are described in a later section, the primary risk associated with MUGA scans is an allergic reaction to the contrast material. Symptoms of an allergic reaction may include nausea, vomiting, diarrhea, irregular heartbeat, rash, swelling, fatigue, disorientation, and/or fainting.

Risks from Lumbar puncture:

The lumbar puncture may cause pain at the site where the needle goes in and the spinal fluid is taken. There is a small risk of infection or bleeding. After the lumbar puncture (LP) you may get a headache. About a third of adults report a headache after an LP. To minimize the risk of a headache, the doctor will use a small needle and may prescribe bed rest for one or more hours after the procedure. If a headache occurs, it is usually mild and can be controlled by bed rest, drinking lots of fluids and a pain pill, such as acetaminophen. Rarely, the headache is severe and may require additional treatment with a "blood patch". In this procedure, a small amount of your own blood is injected into the lumbar puncture site. This procedure is generally effective in stopping the headache. A rare but serious complication of a LP, if it is done when the pressure inside the head is higher than normal (such as when a brain tumor is present), is known as medullary herniation which can result in death. Increased intracranial pressure is very unlikely to be present. The LP will not be done if there are any clinical indications that you have increased intracranial pressure, a skin infection in the lower back area, or bone malformation of the lower back (including severe scoliosis) which would make a LP difficult.

To minimize these risks, the lumbar puncture procedure will be performed by a medical professional specifically trained to do this procedure.

Risks from Radiation:

During your participation in this research study, you will be exposed to radiation from lumbar punctures performed under fluoroscopy guidance, CT scans, a Technetium-99 bone scan, and possibly MUGA scans, if needed. The amount of radiation exposure you will receive from these procedures is equal to approximately 11.19 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 lumbar punctures and scans that you get in this study will expose you to the roughly the same amount of radiation as 37.3 years' worth of background radiation. Being exposed to too much radiation can cause harmful side effects such as an increase in the risk of cancer. The risk depends on how much radiation you are exposed to. Please be aware that about 40 out of 100 people (40%) will get cancer during their lifetime, and 20 out of 100 (20%) will die from cancer. The risk of getting cancer from the radiation exposure in this study is 1.1 out of 100 (1.1%) and of getting a fatal cancer is 0.6 out of 100 (0.6%).

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.

Risks of CT Scans

A CT scan is an X-ray procedure where a high-speed computer is used to make multiple images or pictures of your body. In addition to the radiation risks discussed above, there are also some non-radiation risks associated with this procedure. Sometimes, a contrast dye that contains iodine is administered into one of your veins to improve these images. In some cases, people might have an allergic reaction to this dye. You will be asked to lie still on a table and at times may have to hold your breath for a few seconds in order to avoid blurring the pictures. You may hear a slight buzzing, clicking and/or whirring sounds as the CT scanner moves around your body.

There is a chance of developing an allergic reaction from the contrast material, which may cause symptoms ranging from mild itching or a rash to severe difficulty breathing, shock or rarely, death. The contrast material may also cause kidney problems. The study doctors will do a blood test prior to the scan procedure to confirm that it is safe for you to receive the contrast.

For IV contrast: You may feel discomfort when the contrast material is injected. You may feel warm, flushed, get a metallic taste in your mouth or, rarely, may make you vomit or feel sick to your stomach.

For oral contrast: You may experience vomiting, nausea, cramping, bloating, constipation or diarrhea after drinking the contrast.

Risks of Technetium-99 Bone Scans

This scan is a procedure that uses Technetium 99m to trace cancer that has spread (metastasized) to the bone from the tumor's original location; in this case, from the breast or uterus. In addition to the risks of radiation described above, this test requires administration of the contrast agent. You may experience pain, bruising, and/or infection at the site of injection, or an allergic reaction to the contrast agent.

Risks of MRIs

People are at risk for injury from the MRI magnet if they have some kinds of metal in their body. It may be unsafe for you to have an MRI scan if you have pacemakers or other implanted electrical devices, brain stimulators, some types of dental implants, aneurysm clips (metal clips on the wall of a large artery), metal prostheses (including metal pins and rods, heart valves, and cochlear implants), permanent eyeliner, tattoos, an implanted delivery pump, or shrapnel fragments.

Welders and metal workers may have small metal fragments in the eye. You will be screened for these conditions before having any MRI scan. If you have a question about metal in your body, you should inform the staff. You will be asked to complete an MRI screening form before each MRI scan you have.

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

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

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

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

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

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

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

People with kidney disease are at risk for a serious reaction to gadolinium contrast called "nephrogenic systemic fibrosis (NSF)". This condition always involves the skin and can also involve the muscles, joints and internal organs. NSF has resulted in a very small number of deaths. A blood test of your kidney function may be done within the month before an MRI scan with gadolinium contrast. You will not receive gadolinium for a research MRI scan if your kidney function is below the safe level.

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

Privacy Risks:

The following general points are indirectly related to your participation in the research study.

1. Unanticipated medical information: During the course of this investigation, it is possible (although not likely) that we will obtain unanticipated information about your health or genetic background.

2. Release of medical records. In the course of applying for certain types of insurance (e.g., medical insurance, life insurance, or disability insurance), people are often asked to sign forms that authorize insurance companies to obtain their medical records. If you sign such a release form at some point in the future, it is possible that the insurance company would present this signed release form to the Clinical Center of the National Institutes of Health. In that event, the National Institutes of Health would comply with your request to provide the insurance company with your medical record. It is possible that information contained in your medical record might affect (either favorably or unfavorably) the willingness of the insurance company to sell you insurance. Your employability may also be affected.

3. Release of genetic information:

- Your privacy is very important to us and we will use many safety measures to protect your privacy. However, in spite of all of the safety measures that we will use, we cannot guarantee that your identity will never become known. Although your genetic information is unique to you, you do share some genetic information with your children, parents, brothers, sisters, and other blood relatives. Consequently, it may be possible that genetic information from them could be used to help identify you. Similarly, it may be possible that genetic information from you could be used to help identify them.

- While the controlled-access databases developed for this project will not contain information that is traditionally used to identify you, such as your name, address, telephone number, or social security number, people may develop ways in the future that would allow someone to link your genetic or medical information in our databases back to you. For example, someone could compare information in our databases with information from you (or a blood relative) in another database and be able to identify you (or your blood relative). It also is possible that there could be violations to the security of the computer systems used to store the codes linking your genetic and medical information to you.

- Since some genetic variations can help to predict the future health problems of you and your relatives, this information might be of interest to health providers, life insurance companies, and others. Patterns of genetic variation also can be used by law enforcement agencies to identify a person or his/her blood relatives. Therefore, your genetic information potentially could be used in ways that could cause you or your family distress, such as by revealing that you (or a blood relative) carry a genetic disease.

- There also may be other privacy risks that we have not foreseen.

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.

Questionnaires

These may contain questions that are sensitive in nature. You may refuse to answer any question that makes you feel uncomfortable. If you have concerns after completing the questionnaire, you are encouraged to contact your doctor or the study chair.

Potential Benefits of Participation

The aim of this study is to see if this experimental treatment with temozolomide will prevent development of new brain metastases. We do not know if you will receive personal, medical benefit from taking part in this study. These potential benefits could include prevention of new brain metastases, shrinking of your tumor outside the brain 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 gets worse during treatment
- if you become pregnant
- 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.

If you decide at any time to withdraw your consent to participate in the trial, we will not collect any additional medical information about you. However, per FDA guidelines, information collected on you up to that point may still be provided to Merck or designated representatives. If you withdraw your consent and leave the trial, any samples of yours that have been obtained for the study and stored at the NCI can be destroyed upon request. However, any samples and data generated from the samples that have already been distributed to other researchers or placed in the research databases can**not** be recalled and destroyed.

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 Protocol Review Guide. You may ask your research team for a copy of the Protocol Review 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.

Merck is providing the drugs for this study to NIH without charge. No NIH investigator involved in this study receives payments or other benefits from any company whose drug, product or device is being tested. However, there are some non-NIH collaborators on this study who may receive payments or benefits, limited by the rules of their workplace

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. 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.

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
- Qualified representatives from MERCK & Co., Inc., the pharmaceutical company who produces Temozolomide.

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 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, Stanley Lipkowitz, MD, PhD, lipkowis@navmed.nci.nih.gov, 240-760-6129. 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