Official Title:

A Phase 1 Trial of D2C7-IT in Combination with Atezolizumab in Recurrent WHO Grade IV Malignant Glioma

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Nov 07, 2022

Consent to Participate in a Research Study
ADULT
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PROTOCOL NO.:	Pro00101898 WCG IRB® Protocol #20192802
DATE FINALIZED:	Protocol Version 6.0 Dated 07/12/2022
SPONSOR:	Duke University
INVESTIGATOR:	Daniel Landi, MD The Preston Robert Tisch Brain Tumor Center Duke University Box 31380 Durham, NC, 27710 United States
STUDY-RELATED PHONE NUMBER(S):	Daniel Landi, MD During regular business hours (919) 684-5301 (Office) (919) 206-3405 (Pager) (24 hours) After hours and on weekends and holidays (919) 684-8111 (Ask for Neuro-Oncologist on call)

CONCISE SUMMARY

The purpose of this research study is to determine the safety of administering a single dose of an investigational compound called D2C7-immunotoxin (IT) in combination with an investigational drug called atezolizumab (Tecentriq®) in adults diagnosed with a recurrence of a cancerous brain tumor (malignant glioma). The word "investigational" means the study drug or device or biologic is still being tested in research studies and is not approved by the U.S. Food and Drug Administration (FDA).

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Study participants will receive a single infusion of D2C7-IT in the hospital, which is delivered to the tumor over 3 days through a catheter placed in the brain. Participants will begin receiving intravenous (through a vein) atezolizumab 2 weeks later. Atezolizumab infusions are every 3 weeks. You will be part of this research study for up to two years after your D2C7-IT infusion.

There are risks to the study drugs that are described in this document. Some common risks related to D2C7-IT include: effects related to tumor cells dying (tumor necrosis), effects on normal brain tissue, effects related to catheter placement and removal, effects related to fluid infusion into the brain (intracerebral infusion), and reactions to the D2C7-IT being directly infused in your brain. Some common risks related to atezolizumab include: abnormal immune responses in which your immune system attacks normal organs in your body, tiredness, nausea, constipation, cough, shortness of breath, and decreased appetite.

If you are interested in learning more about this study, please continue reading below.

You are being asked to take part in this research study because you have been diagnosed with a malignant (cancerous) brain tumor that has progressed or recurred. Research studies are voluntary and include only people who choose to take part. Please read this consent form carefully and take your time making your decision. As your study doctor or study staff discusses this consent form with you, please ask him/her to explain any words or information that you do not clearly understand. We encourage you to talk with your family and friends before you decide to take part in this research study. The nature of the study, risks, inconveniences, discomforts, and other important information about the study are listed below.

Please tell the study doctor or study staff if you are taking part in another research study.

A grant from the National Cancer Institute will fund this study, and it is sponsored by Duke University. Portions of Dr. Daniel Landi's and his research team's salaries will be paid by this grant.

WHO WILL BE MY DOCTOR ON THIS STUDY?
If you decide to participate, either the doctor overseeing this study, Dr. Daniel Landi, your doctor here at the Preston Robert Tisch Brain Tumor Center (PRTBTC) at Duke, or a study team member will be in contact with your regular health care provider throughout the time that you are in the study and afterwards, if needed.

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The D2C7-IT technology that is being used in the study has been developed by investigators at Duke and may be licensed to a company outside of Duke. If this technology is commercially successful in the future, Duke and the investigators on this study, including Drs. Darell Bigner, Annick Desjardins, Henry Friedman, Allan Friedman, and John Sampson, may benefit financially.

WHY IS THIS STUDY BEING DONE?
D2C7-immunotoxin (IT) is an investigational compound we are using in this research study. The word "investigational" means that D2C7-IT is still being tested in research studies, and it is not approved by the Food and Drug Administration (FDA). An immunotoxin is a human-made protein that consists of a targeting portion linked to a toxin. The toxin is based on a portion of a common bacteria that the immune system cells will recognize. D2C7-IT is engineered to recognize two receptors, Epidermal Growth Factor wild type (EGFRwt) and Epidermal Growth Factor variant type III (EGFR-vIII). These receptors are expressed in many malignant glioma cells.

Atezolizumab (Tecentriq®) is the other study drug that will be used in this study, and it is currently approved by the FDA for locally advanced or metastatic (spread to other areas of the body) urothelial carcinoma and metastatic non-small cell lung cancer. Atezolizumab is a monoclonal antibody that unblocks "checkpoint" proteins that interfere with the immune system attacking tumor cells.

Based upon our studies with animal models, we believe that combining D2C7-IT with a checkpoint inhibitor, such as atezolizumab, may be effective against brain tumors. The only currently approved treatments for recurrent cancerous brain tumors are Gliadel® (carmustine) wafers or other nitrosoureas, lomustine, a drug called Avastin® (bevacizumab) for glioblastoma, Optune® (NovoTTF) for glioblastoma, or a combination of surgery and re-irradiation.

The current study is supported by grants or donations. However, for this treatment ultimately to be available to all patients beyond research studies, the technology must be developed by a drug company. D2C7-IT was developed by researchers at Duke. If it becomes commercially successful in the future, both Duke and the developers may benefit financially.

The purpose of this study is to determine if D2C7-IT in combination with atezolizumab is safe for patients with recurrent malignant glioma. Patients with recurrent malignant glioma received D2C7-IT alone in an earlier dose-finding study at the Preston Robert Tisch Brain Tumor Center

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(PRTBTC). The dose of D2C7-IT alone decided upon in the earlier study is now being used in combination with the dose of atezolizumab already approved by the FDA for other types of cancer. The safety of combining D2C7-IT and atezolizumab has only been studied in animal models so far.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?
This study may consent up to 40 people, in order to meet the goal of having up to 25 patients with recurrent malignant glioma take part in this study at the Duke University Medical Center (DUMC).

WHAT IS INVOLVED IN THE STUDY?
This is a Phase 1 study to determine the safety of D2C7-IT in combination with atezolizumab. If you agree to be in this study, you will be asked to sign and date this consent form. You will have the following tests and procedures to make sure that you are eligible.

Screening Period:
- Physical exam, including a full neurological examination (brain and nervous system function), and medical history.
- Blood draw (by needlestick) for a complete blood count (CBC), a complete metabolic panel (CMP) to test your liver and kidney function, a blood test to see how quickly your blood clots, a test called lactate dehydrogenase (LDH) to see how much of this protein is in your blood, and a blood test of your white blood cell counts (LSQ) to look at specific white blood cells, and a thyroid profile (about 5 teaspoons [25 mL] of blood).
- Blood pregnancy test, if you are a female of childbearing potential (1 teaspoon of blood). Pregnant women cannot participate in this study.
- Buccal swab (swab of the inside of your cheek using a long Q-tip) to look at antigens on the surface of your cells and tissues.
- Baseline magnetic resonance imaging (MRI) scan of the brain within 1 week of biopsy.

If the results of your screening tests show that you are eligible to take part in this study and you choose to do so, you may undergo several procedures including those listed below.

The study team will request a sample of tissue from your initial biopsy or resection, as well as any other previous biopsies or resections, from the hospital where it was performed. This sample will be tested at Duke for the presence of biological markers related to your immune response to the D2C7-IT infusion. This will help us better understand how D2C7-IT works within your body.

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You will participate in health-related quality of life questionnaires and cognitive testing (evaluations of the ability to think and reason) tests as a baseline.

Immediately after you have had a brain tumor biopsy to confirm the type of recurrent tumor you have and if you are eligible to take part in the study, you will have up a catheter inserted into the location of the tumor (please see additional details in the "Biopsy" and "Placement of Catheter" sections below). It is possible that confirmation of the type of recurrent tumor you have could take up to 1-2 days. During that time, you will remain in the hospital. If the diagnosis of recurrent malignant glioma is not confirmed, the catheter will be removed and you will not continue to take part in the study. If the biopsy confirms recurrent malignant glioma, you will receive a continuous infusion of D2C7-IT over 3 days through the inserted catheter.

Biopsy:
A biopsy is a surgical procedure that your neurosurgeon will explain to you in detail beforehand. After you are taken to the operating room, your scalp will be prepared and washed. During the procedure, the surgeons will remove a few pieces of the tumor, and it will be analyzed in the operating room by a pathologist to determine the type of tumor you have. A portion of the tumor will also be sent to our pathology laboratory for definitive clinical diagnosis. After the pathology department confirms that you have a recurrence of your tumor and completes all of their standard biopsy testing, the study team would like to obtain additional tissue for research testing. To extract this additional tissue, the study team will insert and remove the biopsy needle up to three additional times immediately following your standard biopsy. Tissue leftover from the biopsy, if any, and the tissue collected for additional research testing will be tested at both Duke and laboratories outside of Duke. Molecular genetic tests will be run on tissue designated for research from your biopsy to determine the genetic characteristics of these samples. This testing may provide information to the study team regarding what types of tumors respond best to D2C7-IT and atezolizumab. The genetic studies described here are for research purposes only. Therefore, you will not receive the results from this testing. The research tests are not being used as diagnostic tests for any disease or illness. The use of your leftover tissue for these molecular tests may use up all the remaining tissue, precluding the possibility of further testing.

If you choose not to allow this additional tissue to be extracted for research tests following your standard biopsy, you can still be part of this study. No matter what you choose, it will not affect the care you receive as part of this study or at DUMC.

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Please indicate your choice by placing your initials below on the appropriate line:

_____ "YES, I agree to allow the study team to obtain additional tissue following my biopsy."

_____ "NO, I DO NOT agree to allow the study team to obtain additional tissue following my biopsy."

Placement of Catheter:
Immediately after the biopsy procedure is complete in the operating room, a catheter (small tube) will be placed by the neurosurgeon in and around the tumor with one end of the catheter extending slightly outside of the head. The final decision about target areas for catheter placement will be determined by the neurosurgeon's clinical judgment and the MRI findings. To aid the neurosurgeon in determining the best areas or targets for catheter placement, a computer-based tool developed by Brainlab AG based in Germany may be used. Once the catheter has been placed, you will have a physical and neurological examination, as well as a Computed Tomography (CT) scan. The CT scan is done so that the neurosurgeon can confirm that the catheter is in the best position for the D2C7-IT infusion, enabling the D2C7-IT to go directly to the area of your tumor, once the final diagnosis of malignant glioma is confirmed. This diagnosis could take up to 1 to 2 days. You will remain in the hospital during that time. If the final diagnosis does not confirm that you have recurrent malignant glioma, the catheter will be removed at your bedside and you will no longer continue to take part in the study, meaning you will not receive the D2C7-IT infusion or atezolizumab.

You will have the following tests or procedures after the catheter placement, prior to D2C7-IT infusion:

- Confirmation of tissue diagnosis by pathologist
- A CT of the brain to confirm catheter placement. If it is determined that the catheter needs to be moved, this may be done at the bedside or you may be taken back to the operating room.
- Blood pregnancy test, if you are a female of childbearing potential, within 48 hours prior to receiving the D2C7-IT infusion (1 teaspoon [5 mL] of blood).
- About seventeen teaspoons of blood (about 86.5 mL) will be collected as a baseline to help detect your immune response to tumor antigens (substances that, when introduced into the body, stimulate the production of an antibody) and a part of the D2C7 immunotoxin.

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Study Period:
D2C7-IT Infusion
If the final diagnosis confirms that the tumor is a recurrent malignant glioma, you will receive D2C7-IT infusion while in the hospital. The D2C7-IT will be infused through the catheter for approximately 72 hours in the Neurosciences ICU or Step down unit at Duke Hospital, where you can be closely monitored.

You will be given an antibiotic (for example, vancomycin) before you are given your anesthesia for the biopsy and catheter placement. You will get this antibiotic for the entire duration of the infusion until the catheter(s) are removed. If vancomycin is used, you will need an additional blood test (1 teaspoon or 5 mL) after the third dose, per standard clinical procedures. This will determine the level of the antibiotic in your blood and make sure it is not at a dangerous level for you.

The catheter will remain in place for as long as the D2C7-IT is being infused (approximately 72 hours). The catheter will be used to slowly infuse the study drug into your brain and around the tumor using a pump similar to the pumps used to infuse fluids into your veins. One possible advantage to this slow infusion is that it will increase the amount of coverage to the tumor by slowly coating the area. At the completion of the infusion, the catheters will be removed at your bedside. This could cause some minor discomfort. The wound will be closed with stitches. Once the D2C7-IT has been infused, it cannot be removed from your body.

While in the hospital during and after the D2C7-IT infusion, the following tests or procedures will be required as part of your research participation:

- A physical and neurological examination each day of your hospitalization and before you are discharged, including vital signs
- Two teaspoons (10 mL) of blood for a CBC and a CMP will be collected on each of the three days of your infusion
- One teaspoon (5 mL) of blood for a LDH after the infusion is over
- Additional blood (about 86.5 mL or 17 teaspoons) will be collected at the end of the D2C7-IT infusion to help detect your immune response to tumor antigens and a part of the D2C7 immunotoxin
- CT of the brain after the catheter(s) are removed

You will be observed in the hospital for a minimum of another 6 hours after the catheter(s) are removed.

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Atezolizumab Infusions and D2C7-IT Follow-up:
Approximately 2 weeks (± 1 week) after your D2C7-IT infusion, you will receive the first dose of atezolizumab intravenously over about 60 minutes. Atezolizumab infusions will continue every 3 weeks (± 1 week) for up to 2 years. All atezolizumab infusions after the first one will be given intravenously over about 30 minutes.

At each clinic visit, the following tests or procedures may be done:

- History and physical exam, including a neurologic assessment
- Two teaspoons (10 mL) of blood for a CBC and a CMP
- One teaspoon (5 mL) of blood for a LDH about every 6 weeks (± 1 week) or every other atezolizumab infusion
- One teaspoon (5 mL) of blood for a LSQ at your week 5 study visit
- Pregnancy test, if appropriate
- One teaspoon (5 mL) of blood for a thyroid profile
- MRI of the brain before your week 5 and week 11 study visits, and every 9 weeks thereafter
- Additional blood to help detect your immune response to tumor antigens and a part of the D2C7 immunotoxin (about 86.5 mL or 17 teaspoons of blood approximately 2, 5, 8, 11, 20, and 29 weeks after the end of your D2C7-IT infusion and
- Health-related quality of life questionnaires and cognitive testing 5 and 8 weeks after the end of your D2C7-IT infusion and then 6 months, 1 year, and 2 years after your D2C7 infusion

If you stop receiving atezolizumab infusions at any point during the study due to bad side effects, your schedule of study tests or procedures will be adjusted. You will no longer have blood tests for your thyroid profile or pregnancy, if applicable, unless your study doctor decides they are necessary. After the study visit at about 11 weeks post D2C7-IT infusion, you will only return to clinic for study visits every 9 weeks (coinciding with your MRI visits).

If You Experience Brain Swelling:
In the event that you experience brain swelling after you receive D2C7-IT, your physician may treat you with bevacizumab. Bevacizumab for the purpose of reducing brain swelling is prescribed at a dose that is lower than what is approved for the treatment of brain tumors (7.5 mg/kg every three weeks).

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Bevacizumab is given intravenously (through a vein), and the need for it will be reassessed by your study doctor every nine weeks using an magnetic resonance imaging (MRI) scan.

If your study doctor does not feel it is safe for you to receive bevacizumab, he/she may discuss other interventions, including steroids or surgery, with you to treat the inflammatory response (swelling of the brain) to D2C7-IT.

Details of some of the above tests and procedures are below:

Magnetic Resonance Imaging (MRI) Scans:
You will have several MRIs during the course of the study. MRIs use a magnet and radio waves to make diagnostic medical images of the body. The MRI involves entering a large room in which a magnet is present. You will be placed on a narrow bed and then slid into a small tunnel approximately 6 feet in length and 25 inches in diameter. You will be asked to lie still for about one hour on this bed. You will hear a loud machine-like noise. You may be asked to have a harmless monitoring device applied during the study. During the study, you can have voice contact and physical contact with someone in attendance if you desire. You may be given a dye intravenously (through a vein) in order to enhance the MRI image.

Computed Tomography (CT) Scan:
You will have a CT scan of the brain after the catheter is placed to make sure it is positioned correctly and also when the catheter is removed. CT scans are a way to make x-ray images of the inside of the body. The CT scanner is a doughnut-shaped machine that uses x-rays to create computer pictures that show structures inside your body more clearly than regular x-ray pictures. During the procedure, a technologist will take you into the CT scan room where you will lie down on the patient table (usually on your back) inside of the CT machine. You should get comfortable because it is very important that you not move during certain parts of the test.

During the study, you will be asked to hold your breath so that the pictures will not be blurred. The machine will make some noise, and the table will move during the scan. Also, you may receive signals from the technologist or from the machine about your breathing. Before or during the study, you may be given an injection of a contrast liquid in your vein to allow the radiologist to obtain clearer images of your organs. If you have any discomfort during the test or after the injection, be sure to tell the technologist.

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HOW LONG WILL I BE IN THIS STUDY?
You will remain in this study for up to 2 years, unless your tumor gets larger (progresses), the side effects become too severe, or you or the study team feels it is in your best interest to stop participating. After 2 years, you may still be followed by your study doctor for several years, if he/she feels it is in your best interest and you agree to be followed.

If you stop taking part in the study due to severe side effects from either placement of the catheter(s) or infusion of D2C7-IT/atezolizumab, these side effects could prevent you from continuing with standard of care treatment. Whether or not your tumor progresses, we will continue to track the size of your tumor based on MRI scans taken at Duke or elsewhere. We may request your medical records when you are seen at another hospital.

We will tell you about new information that may affect your health, welfare, or willingness to stay in this study.

You can choose to not participate or to stop participating at any time without penalty or loss of any benefits to which you are otherwise entitled. However, if you decide to stop participating in the study, we encourage you to talk to your doctor first.

ADDITIONAL TISSUE SAMPLE(S) FROM FUTURE TUMOR BIOPSY OR RESECTION
If, at a future date, you have a biopsy or resection, we would like to request a sample of that tissue. This sample would be analyzed for the presence of biological markers related to your immune response to the D2C7-IT infusion. This will help us to better understand how D2C7-IT works within your body. If you agree to allow these tumor samples to be requested and analyzed by initialing below, the study team will contact you at that time to make certain that you still agree.

If you choose not to allow these tumor samples to be taken, you can still be part of this study.

Please indicate your choice by placing your **initials** below on the appropriate line:

_____ "**YES**, I agree to allow the study team to request a sample of tissue from any future biopsy or resection for the analyses described above."

_____ "**NO**, **I DO NOT** agree to allow the study team to request a sample of tissue from any future biopsy or resection for the analyses described above."

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In the event of your death, we would like to a request a *post mortem* (after death) examination of your brain to provide additional information about the study drug infusions. You can still participate in the study if you do not agree to the *post mortem* examination. Your official next of kin will be asked by your treating doctor after your death and will have the right to refuse the *post mortem* examination even if you agree to the exam below. According to North Carolina law, your family members are able to override your wishes about a *post mortem* examination after your death if they disagree with your choice. Therefore, it is important to talk about your wishes now with your family, so that they are aware of how you feel. Your *post mortem* examination results will become part of your permanent medical records. Neither you nor your family will be responsible for the cost of the *post mortem* examination.

Please indicate your choice by placing your **initials** below on the appropriate line:

_____ "**YES**, I agree to a *post mortem* examination if I die while being followed as part of this study."

_____ "**NO**, **I DO NOT** agree to a *post mortem* examination if I die while being followed as part of this study."

WHAT ARE THE RISKS OF THE STUDY?
As a result of your participation in this study, you are at risk for the following side effects. You should discuss these with the study doctor and your regular health care provider if you choose.

D2C7-IT may cause some, all or none of the side effects listed below.

- Effects related to tumor cells dying (tumor necrosis) including
  - Bleeding in the brain (hemorrhage)
  - Brain swelling (+edema) with possible vomiting and headache
  - Need for an additional surgery (craniotomy- a cut in the skull to relieve pressure in the brain)
  - Hydrocephalus (build-up of cerebrospinal fluid in the brain possibly causing confusion, imbalance or decreased coordination, urinary incontinence, headache, seizures, and/or loss of consciousness), which may require the placement of a shunt (a device that relieves fluid build-up)
- Effects on normal brain including:
  - Changes in neurologic function (e.g. ability to think, move, talk, etc.)

- Increased or new seizures
- Inflammation (swelling) of the normal brain
- Injury to blood vessels with stroke-like effects

- Effects related to catheter placement or removal:
  - Pain
  - Bleeding
  - Bleeding when catheter removed that could require surgery
  - Infection
  - Spread of tumor in the brain
- Effects related to fluid infusion into the brain (intracerebral infusion):
  - Brain swelling with altered level of consciousness (alertness), including coma, headache, vomiting, worsening of prior neurologic problems or new neurologic problems
- D2C7-IT-specific adverse effects on the whole body are considered to be unlikely in this study due to the direct infusion into the brain and low dose levels, but may include:
  - Allergic symptoms like rash, fever, chills or hives (Severe allergic reaction, while rare, can result in death)

Risks of Atezolizumab:
Below is a list of known side effects of atezolizumab and the approximate frequency with which they occur.

More Likely (≥ 1 out of 5 or 20% of patients)
- Feeling tired
- Decreased appetite
- Diarrhea
- Nausea

Less Likely (≥ 1 out of 10 or 10% of patients)
- Peripheral edema
- Fever
- Vomiting
- Constipation
- Abdominal pain
- Back or neck pain
- Joint pain

- Itching
- Rash
- Urinary tract infection
- Cough
- Shortness of breath
- Decreased sodium in the blood
- Elevated blood sugar

Uncommon (< 10% of patients)

- Elevated liver function tests
- Elevated phosphate in the blood
- Elevated calcium in the blood
- Elevated magnesium in the blood
- Decreased white blood cells (lymphopenia)
- Decreased red blood cells (anemia)
- Lung infection

Because atezolizumab works with your immune system to fight your cancer, it can cause your immune system to attack normal organs or tissue and affect how they work. These problems can sometimes become serious or life-threatening and can lead to death. Some of the possible side effects related to abnormal immune responses are provided below:

- Lung inflammation or disease (pneumonitis), which could cause new or worsening cough, shortness of breath, and chest pain
- Inflammation of the liver (hepatitis), which could cause yellowing of your skin or the whites of your eyes, severe nausea or vomiting, pain on the right side of abdomen (stomach area), drowsiness, dark urine, bleeding or bruising more easily, and loss of appetite
- Inflammation of the digestive tract (colitis), which could cause diarrhea or increased bowel movements, blood or mucus in your stool, and severe stomach pain or tenderness
- Hormone gland problems, especially the thyroid (base of the neck), adrenal glands (above the kidneys), pancreas (in your abdomen), and pituitary (base of the head). Side effects of hormone glands not working properly include headaches (persistent or unusual), extreme tiredness, weight gain or loss, dizziness or fainting, feeling more hungry or thirsty than usual, hair loss, changes in mood or behavior, feeling cold, constipation, voice becoming deeper, urinating more often than usual, nausea or vomiting, stomach pain

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- Other abnormal immune responses that could affect any organ or part of the body, including the heart, skin, blood, muscles, nervous system, eyes, kidneys, or blood vessels
- Severe infections that could include fever, cough, flu-like symptoms, pain when urinating, frequent urination or back pain
- Severe infusion reactions that could include chills, itching or rash, flushing, shortness of breath, swelling of the face or lips, dizziness, fever, feeling like passing out, back or neck pain

It is possible that the combination of D2C7-IT and atezolizumab may lead to greater risk of inflammation (swelling) in the brain than D2C7-IT alone. The combination of D2C7-IT and atezolizumab and/or study procedures may cause more serious and/or unknown side effects. Many side effects go away shortly after the study drug(s) are stopped; however, in some cases, side effects may be serious, long-lasting, or permanent, and may even result in hospitalization and/or death.

At the beginning of the study, D2C7-IT was given at the dose currently being used in a study of D2C7-IT alone. The dose of D2C7-IT was reduced after three of the first four patients in the study experienced side effects that resulted in atezolizumab needing to be discontinued. These side effects included elevated liver function tests, perforation (tear or hole) in the colon thought to be related to bevacizumab and steroids given for inflammation in the brain, and hydrocephalus (build-up of cerebrospinal fluid in the brain). Since the dose of D2C7-IT was reduced in September 2020, three patients received the lower dose of D2C7-IT in combination with atezolizumab. As of the beginning of April 2021, these 3 patients have not needed to discontinue atezolizumab prematurely.

Risks of Bevacizumab: (The risks below are for a standard dose of bevacizumab used for treating recurrent malignant glioma. The dose used to treat brain swelling in this study is lower.):

More Likely (≥ 1 out of 5 or 20% of patients)
- High blood pressure (hypertension) which may cause headache or blurred vision
- Abdominal Pain

Less Likely (about 4 – 20% of patients)
- Numbness, tingling or pain in the fingers or toes (peripheral sensory neuropathy)

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- Low numbers of white blood cells (neutropenia, leucopenia and lymphopenia) potentially associated with fever. Low white cell count may increase the risk of infection.
- Low numbers of platelets (thrombocytopenia)
- Shortness of breath (dyspnea)
- Diarrhea
- Bleeding from the rectum (rectal hemorrhage)
- Nausea and vomiting
- Pain, including headache and joints pain (arthralgia)
- Alteration in speech (dysarthria)
- Constipation
- Mucosal inflammation or inflammation of the mouth (stomatitis)
- Protein in the urine
- Nose bleed (epistaxis)
- Lack of energy, weakness (asthenia, fatigue), or dizziness
- Loss of appetite (anorexia), or heartburn
- Body water loss (dehydration)
- Fever (pyrexia)
- Runny nose (rhinitis), stuffy nose, hoarseness, or cough
- Dry skin, flaking and inflammation of the skin (exfoliative dermatitis), change in skin color (skin discoloration)
- Change in the sense of taste (dysgeusia)
- Problems with the eyes (eye disorder), tearing (lacrimation increased)
- Low numbers of red blood cells (anemia) which may require blood transfusion
- Abnormal heartbeat which may cause palpitations or fainting
- Internal bleeding which may cause black tarry stool, vomit in blood, coughing up blood, or blood in urine
- Delay in healing of wounds or spontaneous opening of wounds. Fatal outcomes have been reported.
- Damage to jaw bone which may cause loss of teeth
- Allergic reaction during or after infusion of bevacizumab which may cause fever, chills, rash, itching, hives, low blood pressure, wheezing, shortness of breath, swelling of the face or throat
- Blood clot in limbs or lungs which may cause swelling, pain or shortness of breath
- Infection, presence of bacteria in the blood (sepsis), collection of pus in tissue or organs (abscess)

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Occasional (3% or less of patients)

- A tear or a hole in the gut (perforation of the gastrointestinal tract)
- Abnormal tube-like connection (fistula) between internal organs such as the nose, throat, lungs, esophagus, rectum or vagina that are not normally connected. These conditions may cause serious infections or bleeding and require surgery to repair.
- Bleeding (hemorrhage), including bleeding associated with the tumor
- Clogging of a vessel in the lung (pulmonary embolism)
- Blocking of the arteries by a blood clot, including stroke (cerebral vascular accident) or heart attack. This risk is significantly increased in patients who are elderly or with a history of diabetes.
- Heart failure (cardiac failure congestive), especially in patients who have taken certain chemotherapy treatments in the past (doxorubicin or mitoxantrone) and rapid beating of the heart (supraventricular tachycardia)
- Rapid beating of the heart (supraventricular tachycardia)
- Blood clots in the veins (deep vein thrombosis)
- Abdominal pain
- Blockage in the intestine (ileus, intestinal obstruction)
- Pain, tenderness, or blistering on the fingers or feet (hand-foot syndrome, palmar-plantar erythrodysesthesia syndrome)
- Reduced consciousness, sleepiness, feeling tired (somnolence, lethargy)
- Low levels of oxygen in the blood (hypoxia)
- Fainting (syncope)
- Gastrointestinal disorder
- Voice changes, hoarseness (dysphonia)
- Muscular pain (myalgia) and muscular weakness
- Flesh-eating bacteria syndrome, an infection in the deep layers of the skin
- Kidney damage which may require dialysis

Uncommon (0.1% to Less than 1% of patients)

- Abnormal connection between the windpipe (trachea) and the esophagus (the tube that connects the mouth to the stomach) (tracheo-esophageal fistula)
- A hole in the gut lining of the stomach or duodenum (gastro-intestinal ulcer)

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Rare (0.01% to Less than 0.1% of patients)

- Reversible posterior leukoencephalopathy syndrome: this may include symptoms of impaired brain function (headaches, vision changes, confusion, or seizures), and often, high blood pressure

Very Rare (Less than 0.01% of patients)

- Hypertensive encephalopathy: this may include symptoms of impaired brain function (headaches, vision changes, confusion, or seizures), and often, high blood pressure

Frequency Unknown

- Lesion in the gums with an exposed jawbone that does not heal and may be associated with pain and inflammation of the surrounding tissue (osteonecrosis of the jaw) in particular when treated with "bisphosphonate drugs" in this trial or in the recent past.
- A hole in the gallbladder (gallbladder perforation)
- A hole in the nasal passage (nasal septum perforation)
- Abnormalities to the fetus/unborn child when bevacizumab is given during pregnancy

In trials for colorectal cancer using bevacizumab and chemotherapy, female subjects had a 32% higher incidence of ovarian failure with early menopause (loss of menstrual cycle) and sterility (inability to have children) than subjects using chemotherapy alone.

Risk from CT Scans for Catheter Placement:
If you take part in this research, you will have one or more medical imaging studies which use radiation. The tests or treatments you will have include two head CT scans. The first CT scan will help the study doctor accurately determine where the catheter should be placed, and the second will check if the planned catheter placement was done correctly and there are no complications. To give you an idea about how much radiation you will get, we will make a comparison with an every-day situation. Everyone receives a small amount of unavoidable radiation each year. Some of this radiation comes from space and some from naturally-occurring radioactive forms of water and minerals. This research gives your body the equivalent of about 3 extra years' worth of this natural radiation. The radiation dose we have discussed is what you will receive from this study only, and does not include any exposure you may have received or will receive from other tests.

A possible health problem seen with radiation exposure is the development of a second cancer later in life. This extra cancer risk is higher at younger ages and for girls and women. The extra

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lifetime risk of dying of a fatal cancer due to the radiation exposure from this research is very low. At such low radiation exposures, scientists disagree about the amount of risk. These estimates are very uncertain, and there may be no extra risk at all.

Risk from MRI Scan:
There have been no ill effects reported from exposure to the magnetism or radio waves used in this test. However, it is possible that harmful effects could be recognized in the future. A known risk is that the magnet could attract certain kinds of metal. Therefore, we will carefully ask you about metal within your body (this includes certain dyes found in tattoos). If there is any question about potentially hazardous metal within your body, including medical implants, devices such as pacemakers and internal defibrillators, or certain dyes found in in tattoos. We will also keep the examining room locked so that no one carrying metal objects can enter while you are in the scanner.

If there is any question about potentially hazardous metal within the body, you will not undergo the MRI. This may exclude you from participation in this research study. The MRI involves entering a large room in which a magnet is present. You will be placed on a narrow bed and then slid into a small tunnel approximately 6 feet in length and 25 inches in diameter. You will be asked to lie still for about one hour on this bed. You will hear a loud machine-like noise. You may be asked to have a harmless monitoring device applied during the MRI. During the MRI, you can have voice contact and physical contact with someone in attendance if you desire. Let the study doctor know if you have a fear of enclosed spaces.

The most common side effects of the MRI contrast agents are local warmth/pain at the injection site, nausea and/or vomiting. Serious allergic reactions are very rare, may occur and may be life-threatening.

A rare but serious adverse reaction has been observed in patients that received a gadolinium-based contrast material during MRI examinations, a reaction called nephrogenic systemic fibrosis (NSF). Patients with kidney disease are at increased risk of developing NSF. NSF may cause skin thickening, joint pain and/or swelling. In rare cases, NSF can lead to lung and heart problems and cause death. To minimize the likelihood that you will be affected, you will have a blood test to measure your kidney function. If your blood test is abnormal, you will not be permitted to receive gadolinium.

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You may have a number of MRI scans or CT scans that are part of the regular care for your condition, and you would have them whether or not you participate in this research. These studies will not add to the risk of the research. However, if you have concerns about CT radiation and MRI safety issues, you should discuss them with your physician.

Risk of Mouse Antibodies:
This drug is a protein made from mouse cells. There is the possibility that persons who participate in this research will develop antibodies to mouse proteins. If antibodies are formed, they may reduce the effectiveness of medicines developed from mouse proteins, though this is unlikely to occur. The antibodies may also interfere with certain laboratory tests. Medicines that contain mouse proteins are used to treat diseases such as rheumatoid arthritis, Crohn's disease, and cancer. This means that there is a very small possibility that you may not be able to receive other medicines in the future that contain mouse proteins or that the effectiveness of the medicines may be diminished. You should tell your doctors in the future that you have received a drug that contains mouse proteins.

Risks of Additional Tissue Sampling During Brain Tumor Biopsy:
Prior to infusion of the study drug, you will have a standard biopsy to confirm that you have recurrence of your tumor. After obtaining tissue for the pathology department to confirm that you have a recurrence of your tumor, you will have additional tissue extracted for research testing, if you agree to this. A biopsy can result in swelling or bleeding in the brain. Risks can also include pain at the biopsy site, bleeding, infection, and seizures. In very rare cases, the biopsy can lead to new or worsening neurological deficit (ability to think, move, feel, speak, see), stroke, coma, or death. Having additional tissue extracted for research testing following your standard biopsy may increase these risks and may extend the time that you are under anesthesia.

Reproductive Risks
For women: Atezolizumab may cause harm to a developing pregnancy. In addition, the effects of D2C7-IT in developing pregnancies or breastfeeding infants are not known. Women who are pregnant, planning a pregnancy, or breastfeeding are not allowed to participate in studies of these drugs.

If you are a woman who could possibly become pregnant (you have not completed menopause, or you have not had a hysterectomy and/or both tubes and/or both ovaries removed) and you have a partner who is able to father children, a blood pregnancy test will be done at the

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beginning of the study and it must be negative in order to continue. In women 40 years old and older, blood pregnancy tests can sometimes give a false positive or indeterminate result and additional testing may be required. A blood pregnancy test will be repeated within 48 hours prior to receiving the D2C7-IT infusion and it must be negative.

You and your partner must agree to either abstain completely from vaginal intercourse for the duration of the study and for 6 months afterwards, or use effective methods of contraception for the same length of time. Effective methods include (a) partner vasectomy, (b) bilateral tubal ligation, (c) intrauterine devices (IUDs), (d) hormonal methods that do not contain estrogen (some birth control pills, implants, injections), or (e) barrier methods (condoms, diaphragms, cervical caps) with spermicide. Because hormonal methods containing estrogen increase the risk of blood clots, they are generally not considered safe when other drugs, such as bevacizumab, also increase this risk. If you are not using one of these methods, your study doctor will discuss options with you, given your medical condition, your personal preferences, and the level of protection required by this study.

Because no method of birth control is 100% effective, you should notify your study doctor if you think there is any chance you could be pregnant. If pregnancy is confirmed, the study drugs will be stopped, but your study doctor will continue to follow you to collect information on your health during pregnancy and, if appropriate, the health of the baby.

For men: The effects of the study drugs on a developing pregnancy that began while the father was taking the drug are not known. If you have a partner who could possibly become pregnant (she has not completed menopause, or she has not had a hysterectomy and/or both tubes and/or both ovaries removed), you must agree to either abstain completely from vaginal intercourse for the duration of the study and for 6 months after your last dose of study drug, or use effective methods of contraception for e the same length of time. Effective methods include (a) vasectomy, (b) bilateral tubal ligation, (c) intrauterine devices (IUDs), (d) hormonal methods (birth control pills, implants, injections, patches, vaginal rings), or (e) barrier methods (condoms, diaphragms, cervical caps) with spermicide. If you and your partner are not using one of these methods, your study doctor will discuss options with you.

You should inform your partner about your participation in this study and the potential risks to a pregnancy. If she does become pregnant, you should notify your study doctor immediately. Your partner will be asked for permission to collect information on her health during the pregnancy and, if appropriate, the health of the baby.

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Risks of Drawing Blood:
Risks associated with drawing blood from your arm include momentary discomfort and/or bruising. Infection, excess bleeding, clotting, or fainting are also possible, although unlikely.

Drug and Food Interactions:
For your safety, you must tell the study doctor or nurse about all the prescribed medical foods and drugs, herbal products, over-the-counter (OTC) drugs, vitamins, natural remedies, and alcohol that you are taking before you start the study and before starting to take any of these products while you are on the study.

Risks of Genetic Testing:
It is possible that this study will identify information about you that was previously unknown, such as disease status or risk. There are no plans to provide this information to you or your physician, unless the information indicates that you may be at risk for a serious illness known at the time of testing to be treatable. In that case, we will attempt to notify you using the contact information you have provided, so that you can speak with your study doctor. The study team will not provide this information in a voice mail, email, or otherwise prior to contacting you. Please notify us of any change in your contact information.

If you do not want to be notified of any incidental findings, please initial below.

_____ Please do not notify me of any incidental findings obtained from this research.

If you prefer, we can ask you at the time of notification whether or not you want to receive incidental findings information. In this case, please initial below.

_____ Please ask me at the time of notification whether or not I want to receive incidental findings information.

If at any time during or after the study you change your mind about whether or not you would like to be notified, you can contact us at 919-684-5301.

After providing the information to you, your study doctor may arrange for you to meet with him or her and possibly a genetic counselor or refer you to another appropriate health care provider to review the incidental findings information with you or your physician.

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Potential Risks and the Genetic Information Non-Discrimination Act (GINA):
There is a potential risk of loss of confidentiality. Every effort will be made to protect your confidential information, but this cannot be guaranteed. The genetic information obtained as a result of your participation in this research will be included in your medical record. Information from which you may be personally identified will be maintained in a confidential, secure location at DUHS, accessible only by authorized members of the study team, and will not be disclosed to third parties except as described in this consent form, with your permission, or as may be required by law. The Genetic Information Nondiscrimination Act (GINA) is a Federal law that will protect you in the following ways:

- Health insurance companies and group plans may not request genetic information from this research;
- Health insurance companies and group plans may not use your genetic information when making decisions regarding your eligibility or premiums;
- Employers with 15 or more employees may not use your genetic information when making a decision to hire, promote, or fire you or when setting the terms of your employment.

GINA does not protect you against genetic 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 genetic condition or disease.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?
If you agree to take part in this study, there may be direct medical benefit to you. A possible benefit would be an improvement and reduction in the amount of disease you have but this cannot be guaranteed. We hope that in the future the information learned from this study will benefit other people with your condition.

WHAT ALTERNATIVES ARE THERE TO PARTICIPATION IN THIS STUDY?
Instead of being in this study, you have the following alternatives:
- You could choose to have a biopsy without catheter placement and the subsequent infusion of D2C7-IT.
- You could choose to receive alternative investigational drugs.
- You could choose to receive an alternative chemotherapy treatment with or without comfort care.

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- You could choose to receive the standard therapies for this disease (recurrent malignant glioma), which currently includes Gliadel® (carmustine) wafers or other nitrosoureas, treatment with a drug called Avastin® (bevacizumab) for glioblastoma, Optune® (NovoTTF) for glioblastoma, or a combination of surgery and re-irradiation.
- You could choose to receive no therapy at this time and receive care to help you feel more comfortable. If you choose this option, you may reconsider at any time, and this decision will in no way affect the regular care that you receive.

Enrollment in this study may preclude or delay receipt of standard therapies with known benefit. Please talk to your doctor about these and perhaps other options.

WILL MY INFORMATION BE KEPT CONFIDENTIAL?
Participation in research involves some loss of privacy. We will do our best to make sure that information about you is kept confidential, but we cannot guarantee total confidentiality. Your personal information may be viewed by individuals involved in this research and may be seen by people including those collaborating, funding, and regulating the study. We will share only the minimum necessary information in order to conduct the research. Your personal information may also be given out if required by law.

Daniel Landi and his study team may report the results of your study-related laboratory tests and scans to the reviewers listed below, in order to meet federal or state regulations. Reviewers may include representatives from the Food and Drug Administration (FDA), NIH or the National Cancer Institute (NCI), BrainLab AG, Duke Cancer Institute (DCI), Cancer Therapy Evaluation Program (CTEP) (the supplier of atezolizumab) and its contractors, Genentech, Inc. (the manufacturer of atezolizumab), Duke Office of Audit, Risk, and Compliance (OARC) office, the Brain Tumor Center Data Safety Monitoring Board (DSMB), the WCG IRB, and the Duke University Health System Institutional Review Board (IRB). These would include laboratory tests, such as your blood counts and tests to measure the function of your liver and kidneys, pathology tests, and scans, as well as the dates of such tests and scans. If any of these groups review your research record, they may also need to review your entire medical record.

As part of the study, the study team will request a sample of tissue from your initial biopsy or resection, as well as any other previous biopsies or resections, from the hospital where it was performed. In doing so, the study team may provide a copy of your signed consent form to the hospital, which shows both your name and Duke medical record number. This is necessary, in order to request your tissue sample for this research study.

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Some of the tissue from your biopsy may be sent to a company outside of Duke for genetic testing.

As part of this study, Dr. Landi and his study team will ask you to have certain tests and scans. Some of these blood tests and scans would have been done as part of your regular care. She will use these test results both to treat you and to complete this research. These test results will be recorded in your medical record and may be reported to the NIH. Results of tests and studies done solely for this research study and not as part of your regular care may also be included in your medical record.

As part of this study, Dr. Landi or his study team may disclose the following information about you to the company who has licensed the D2C7-IT technology from Duke: diagnosis and diagnosis date, neurologic findings, tumor biomarker assessments, dates related to your treatment, treatment types, duration and response to treatment, pictures of your MRI scans (not the actual scans), and lab data. This data, however, will not contain any information that could be used to identify you directly, such as your name or medical record number, and will be labeled with study ID number only.

The study results will be retained in your research record for at least six years after the study is completed. At that time, either the research information not already in your medical record will be destroyed or information identifying you will be removed from such study results at DUHS. Any research information in your medical record will be kept indefinitely. This information may be further disclosed by the supporters of this study. If disclosed by the supporters, the information is no longer covered by federal privacy regulations. If this information is disclosed to outside reviewers for audit purposes, it may be further disclosed by them and may not be covered by federal privacy regulations.

While the information and data resulting from this study may be presented at scientific meetings or published in a scientific journal, your identity will not be revealed.

Some people or groups who receive your health information might not have to follow the same privacy rules. Once your information is shared outside of DUHS, we cannot guarantee that it will remain private. If you decide to share private information with anyone not involved in the study, the federal law designed to protect your health information privacy may no longer apply to the information you have shared. Other laws may or may not protect sharing of private health information.

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WHAT ARE THE COSTS TO YOU?
You or your insurance provider will be responsible and billed for all costs related to your routine medical care, including copayments and deductibles. Routine medical care services are those that you would have received for your condition if you were not participating in this research study and include the biopsy scheduled prior to D2C7 infusion and related hospital stay. If you are treated with bevacizumab, you or your insurance carrier will also be responsible and billed for the cost of this drug. While you or your insurance provider will not be charged for the cost of atezolizumab, you or your insurance provider will be charged for costs related to the Outpatient Treatment Room where these infusions are given. Not all services are covered by insurance. Some procedures or scans may require pre-authorization by your insurance plan. We will notify you if we learn that a service is not covered by your insurance plan as part of the pre-authorization process. If it is not covered, you will be responsible for paying for it. The amount of your out-of-pocket expense will depend on your insurance plan. For beneficiaries with Medicare Advantage Plans, traditional Medicare is billed for the routine cost of a research study. You may have more or higher co-pays than with a Medicare Advantage plan. Please discuss the costs of the study with Dr. Landi. At your request, a Financial Counselor in the clinic may provide you with an estimate of costs for routine services.

The Cancer Therapy Evaluation Program (CTEP) has agreed to provide atezolizumab free of charge to you. It is possible that the atezolizumab may not continue to be supplied while you are on the study. Although not likely, if this occurs, your study doctor will talk to you about your options.

We will monitor your DUHS patient care charges to make sure that costs are directed appropriately. If you have any questions or concerns about appropriate billing, contact your study team coordinator so that he/she can help find a resolution.

You will not be responsible for the costs of the following research tests or procedures:
1. Study drug, D2C7-IT
2. Study drug, atezolizumab
3. Catheter used to infuse the study drug
4. Tubing and pumps used to infuse the study drug
5. Molecular genetic testing on tumor tissue leftover from your biopsy
6. Blood tests for immune monitoring

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7. LSQ, a blood test that helps investigators understand how your immune system is functioning
8. LDH, a blood test that sees how much of this protein is in your blood
9. Buccal swab that looks at antigens on the surface of your cells and tissues

WHAT ABOUT COMPENSATION?
You will receive no payment for taking part in this study.

There are also no plans to provide any compensation to you for any new products or discoveries that may result from your participation in this research or from the use of your blood or tumor samples.

WHAT ABOUT RESEARCH RELATED INJURIES?
Immediate necessary medical care is available at Duke University Medical Center in the event that you are injured as a result of your participation in this research study. However, there is no commitment by Duke University, Duke University Health System, Inc., your Duke physicians, or the study supporter, NCI CTEP, to provide monetary compensation or free medical care to you in the event of a study-related injury.

For questions about the study or research-related injury, contact Dr. Daniel Landi at (919) 684-5301 during regular business hours and at (919) 206-3405 after hours and on weekends and holidays.

WHAT ABOUT MY RIGHTS TO DECLINE PARTICIPATION OR WITHDRAW FROM THE STUDY?
You may choose not to be in the study, or, if you agree to be in the study, you may withdraw from the study at any time. If you withdraw from the study, no new data about you will be collected for study purposes unless the data concern an adverse event (a bad effect) related to the study. If such an adverse event occurs, we may need to review your entire medical record.

Your decision not to participate or to withdraw from the study will not involve any penalty or loss of benefits to which you are entitled, and will not affect your access to health care at Duke. If you do decide to withdraw, we ask that you contact Dr. Landi in writing and let him know that you are withdrawing from the study. His mailing address is The Brain Tumor Center, Duke University Medical Center, Box 31380, Durham, NC 27710. Dr. Landi may ask you to complete the tests that would ordinarily occur when a person completes the study.

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We will tell you about new information that may affect your health, welfare, or willingness to stay in this study.

Your doctor may decide to take you off this study if your condition gets worse, if you have serious side effects, or if your study doctor determines that it is no longer in your best interest to continue. Although unlikely, it is possible that NCI CTEP may stop providing the study drug atezolizumab. Regulatory agencies, such as the FDA or Western IRB, may stop this study at any time without your consent due to reasons such as concern for patient safety. If this occurs, you will be notified and your study doctor will discuss other options with you.

If you agree to allow your tissue to be kept for future research with identifying information that could link your sample to you, you are free to change your mind at any time. We ask that you contact Dr. Landi in writing and let him know you are withdrawing your permission for your identifiable tissue to be used for future research. His mailing address is above. At that time, we will ask you to indicate in writing if you want the unused identifiable tissue destroyed or if your samples (having all identifying information removed that would link the sample to you) could be used for other research.

However, your samples and/or data may be stored and shared for future research without additional informed consent if identifiable private information, such as your name and medical record number, are removed. If your identifying information is removed from your samples or data, we will no longer be able to identify and destroy them.

The use of your samples may result in commercial profit. You will not be compensated for the use of your samples.

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

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?
For questions about the study or a research-related injury, or if you have problems, concerns, complaints, questions or suggestions about the research, contact Dr. Daniel Landi at (919) 684-5301 during regular business hours and pager number (919) 206-3405 after hours and on weekends and holidays. After hours and on weekends and holidays, you can also call (919) 684-

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8111 and ask for the Neuro-Oncologist on call.

If you have questions about your rights as a research subject or if you have questions, concerns, input or complaints about the research, you may contact:

WCG IRB
1019 39th Avenue SE Suite 120
Puyallup, Washington 98374-2115
Telephone: 855-818-2289
E-mail: researchquestions@wcgirb.com

WCG IRB is a group of people who perform independent review of research.

WCG IRB will not be able to answer some study-specific questions, such as questions about appointment times. However, you may contact WCG IRB if the research staff cannot be reached or if you wish to talk to someone other than the research staff.

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STATEMENT OF CONSENT
"The purpose of this study, procedures to be followed, risks and benefits have been explained to me. I have been allowed to ask questions, and my questions have been answered to my satisfaction. I have been told whom to contact if I have questions, to discuss problems, concerns, or suggestions related to the research, or to obtain information or offer input about the research. I have read this consent form and agree to be in this study, with the understanding that I may withdraw at any time. I have been told that I will be given a signed and dated copy of this consent form."

Signature of Subject	Date	Time
Signature of Person Obtaining Consent	Date	Time

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