Official Title: DERIVe: DC Migration Study to Evaluate TReg Depletion In GBM Patients with and without Varlilumab

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Form
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DUKE UNIVERSITY HEALTH SYSTEM

Consent to Participate in a Research Study
DERIVe: DC Migration Study to Evaluate TReg Depletion In GBM Patients with and without Varlilumab

IRB APPROVED
AS MODIFIED
Jun 22, 2022

TITLE: DERIVe: DC Migration Study to Evaluate TReg Depletion In GBM Patients with and without Varlilumab

PROTOCOL NO.: Pro00082570
WCG IRB Protocol #20170764

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CONCISE SUMMARY

The purpose of this study is to see if Tetanus-diphtheria (Td) pre-conditioning of pp65, a cytomegalovirus (CMV) protein present on brain tumor cells, loaded dendritic cell (DC) investigational vaccine extends overall survival in patients with glioblastoma (GBM) and to evaluate the safety of a drug called Varlilumab in combination with this investigational vaccine. To achieve this goal, participants will be randomized (like drawing numbers out of a hat) to one of three groups: pp65 CMV DC vaccines with unpulsed (unmodified) DC pre-conditioning, pp65 CMV DC vaccines with Td pre-conditioning, or pp65 CMV DC vaccines with Td pre-conditioning and Varlilumab. You will undergo leukapheresis, and may need to do so more than once if needed, to obtain cells to prepare the pp65 CMV DC vaccine. Leukapheresis is a procedure in which blood is collected into a machine that removes white blood cells and then returns the remainder of the blood back to the individual. The leukapheresis procedure is not typically associated with any discomfort or pain. If your glioblastoma is unmethylated (a biomarker of your tumor), you will receive one cycle of temozolomide (TMZ); otherwise, you will receive TMZ throughout all of your vaccine cycles. If your tumor does not return, you will be on this study for up to approximately 21 months to receive a total of 10 pp65 CMV DC

vaccines. This study requires you to return to Duke more frequently than would be required if you were receiving standard of care treatment for your tumor.

Possible benefits of your participation in this study include improvement in the symptoms of your disease and/or delayed growth of your tumor and/or lengthening the time of your survival, but this cannot be guaranteed. Your disease may worsen while on this study and you may have increased risks associated with the study vaccine or procedures. Please continue reading the consent form below to learn more about the study, associated risks, and benefits.

You are being asked to take part in this research study because you have a malignant brain tumor called glioblastoma. 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.

Dr. Annick Desjardins will conduct the study and it is funded by the National Institute of Health. Portions of Dr. Desjardins' research team's salaries are being paid by these funds. The CMV (cytomegalovirus) vaccine technology used in this study was developed by Drs. John Sampson, Gary Archer, and others at Duke and, if successful, both Duke and the developers could benefit financially. This technology, including the use of the tetanus-diphtheria (Td) vaccine, has been licensed to a Duke start-up company, Annias Immunotherapeutics. Duke University and Drs. Sampson and Archer have an equity interest (stocks and/or options) in the company. Celldex Therapeutics is providing a drug used in this study called Varlilumab. Dr. John Sampson has a consulting relationship with Celldex Therapeutics.

WHO WILL BE MY DOCTOR ON THIS STUDY?
Dr. Annick Desjardins is the doctor overseeing this study. If you decide to participate, Dr. Desjardins will either be your doctor for the study or she will work closely with your doctor at Duke University Medical Center (DUMC). Dr. Desjardins and the study team, including your doctor at DUMC, will be in contact with your regular health care provider throughout the time that you are in the study and afterwards, if needed.

WHY IS THIS STUDY BEING DONE?
The purpose of this study is to learn whether the study vaccine, called pp65 CMV dendritic cells, can activate your immune (protection) system to fight off the tumor cells in your brain. This study vaccine is investigational, which means that it is not approved by the US Food and Drug Administration (FDA) and is still being tested in research studies.

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It is believed that the body's immune system can attack tumor cells and kill them. This is thought to be due to immune cells called T-lymphocytes (T-cells), which can recognize proteins on the surface of tumors as a signal to attack and fight the cancer. In most patients with advanced cancer, the immune system does not adequately destroy the tumor. One reason the immune system may not be able to destroy the tumor is because the immune cells (T-cells) are not stimulated enough. Before your T-cells can become active against tumor cells, they require strong stimulation. There are "stimulator" cells in the body called Dendritic Cells (DCs) that can take up proteins released from cancer cells and present pieces of these proteins (called peptides) to T cells to create this strong stimulation.

The vaccine for this study is made of DCs that are "pulsed" or loaded with genetic material called RNA (ribonucleic acid), which stimulates the DCs to change the RNA into a protein called pp65 CMV. RNA is made from DNA. RNA is a genetic material that has a major role in making proteins. Proteins are the building blocks of your body, cells, and organs.

The pp65 CMV protein is produced by a common virus called Cytomegalovirus (CMV) that 70-80% of us have been exposed to in our lifetime. Recently, we have found that this virus is present (hides) in many malignant brain tumors. Brain tumors are very aggressive and, for reasons we do not yet understand, are difficult for the body to attack. This study examines whether DCs targeting the CMV virus may help prevent your tumor from growing. It is hoped that by injecting the pp65 CMV DC vaccine into your skin, your immune system will be activated against the CMV protein and attack the tumor cells in your brain. Use of a vaccine that stimulates your immune system is called immunotherapy.

Previous research studies have been done on humans using CMV pp65 DC vaccine here at Duke for brain tumors. No serious side effects have been reported. In addition, patients have received DCs loaded with other substances at this and other institutions for the treatment of a variety of different tumors. Again, no serious side effects have been reported. The effectiveness of this type of therapy in treating tumors is unknown at the present time and is the reason for research studies such as this one.

This study is also examining whether receiving Tetanus-diphtheria (Td) immunization before your DC vaccine (called Td pre-conditioning) helps activate the immune response to DC vaccines. Td is a vaccine composed of deactivated (dead) tetanus and diphtheria toxins. It works by causing an immune response by producing antibodies (immune system proteins) so that the body can recognize antigens from tetanus and diphtheria toxins if they are ever introduced into the body. Previous trials have suggested that giving the Td pre-conditioning prior to immunotherapy may help improve the effectiveness of the DC vaccine by activating the immune response. This study will further examine whether Td pre-conditioning helps activate the immune response.

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Some people in this study will also receive Varlilumab, which is a drug that interacts with a protein called CD27 that is expressed on cells in your immune system. The CD27 protein is involved in stimulating the immune system and Varlilumab is thought to promote activation of immune cells (T-cells) that attack the tumor. Varlilumab is still being tested in research studies and is not approved by the U.S. Food and Drug Administration (FDA).

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?
Approximately 112 people will take part in this study at Duke University Medical Center.

WHAT IS INVOLVED IN THE STUDY?
If you agree to be in this study, you will be asked to sign this consent form. In order for you to be eligible for this study, you have already undergone surgery to remove your brain tumor and have had the prescreening blood test. We will need to review your pathology report from your brain tumor surgery to confirm that the brain tumor you have is a Grade IV glioblastoma.

You will have the following tests and procedures to make sure that you are eligible:

- Physical exam, neurologic exam, and medical history
- Vital signs (such as pulse, temperature, and blood pressure)
- Blood tests, including a complete blood count (CBC) and a complete metabolic panel (CMP) to test your liver and kidney function (about 2 teaspoons of blood)
- Blood test (1 teaspoon) to determine whether your blood is positive for CMV (Cytomegalovirus)
- Magnetic Resonance Imaging (MRI) of the brain
- Pregnancy test, if you are a female of child-bearing potential (1 teaspoon of blood)

During the process where your eligibility for the study is being determined, the study team will confirm that archived (stored) tissue is available from your surgery. A small section of your archived tumor will be sent from the pathology laboratory, where the sample is stored, to a laboratory that will test the tissue to determine certain characteristics about your cancer. Your tissue will be tested for a biomarker that is referred to as O6-methylguanine-DNA methyltransferase (MGMT), if this test was not already performed on your tumor tissue. MGMT is a gene that has been shown to be important in predicting the response of glioblastoma to the chemotherapy drug temozolomide (TMZ). Tumors with unmethylated MGMT do not respond as well to TMZ as tumors with methylated MGMT. Your tumor tissue may also be tested for the pp65 CMV protein and a gene called Isocitrate Dehydrogenase 1 (IDH1).

Leukapheresis
If you decide to participate in the study, you will undergo a procedure called leukapheresis at the Duke University Medical Center Apheresis Unit. Leukapheresis is a medical procedure by

which large numbers of white blood cells can be removed from your circulation. The purpose of this procedure is to obtain white blood cells to make the dendritic cells (DCs) for your vaccine. Leukapheresis is not a standard procedure for brain tumor therapy. Leukapheresis requires the insertion of a needle into the veins of both arms, after which you lie on a bed for about 4 hours while blood is collected, much like in a standard blood donation. The main difference is that only the white blood cells are collected, while the red blood cells are returned to your body. A portion of the removed white blood cells will be used to make the DCs for the vaccine. If you do not have sufficient venous access for the leukapheresis, a temporary intravenous catheter may need to be inserted in a deeper vein (central venous catheter).

During leukapheresis, a medication (called citrate) is added to the blood while in the machine to keep the blood from clotting in the tubing. You will be instructed to take Tums, 2 tablets three times a day and at bedtime the day before and the day of the leukapheresis procedure. This is to prevent you from getting hypocalcemia (low calcium in your blood) from the citrate used during leukapheresis. Within 2 days before the leukapheresis, you will have blood drawn for a complete blood count (CBC), a complete metabolic panel (CMP) to test your liver and kidney function, and a pregnancy test (if you are a female of child-bearing potential). Prior to leukapheresis, you will also have about 2 teaspoons of blood taken for immunologic tests.

If you underwent leukapheresis as part of another companion study titled "***Preliminary Testing and/or Procedures for Potential Clinical Trial Participants of the Preston Robert Tisch Brain Tumor Center"*** the vaccines manufactured as part of that study will be used in the current study and any unused vaccine products will be handled as you indicated in the companion study.

Radiation Therapy and Temozolomide (TMZ)
You will receive radiation therapy and the chemotherapy drug TMZ for about 6 weeks. This is standard treatment for people with your type of tumor. You will start radiation therapy within about 6 weeks of your surgery. Temozolomide or Temodar® is an FDA-approved anti-cancer drug and will be given to you by your doctor as part of your standard care. TMZ is taken daily during radiation therapy. It is a capsule that you take by mouth; the actual number of capsules you take will vary depending upon your height and weight. It should be taken in a fasting state (nothing to eat for one hour prior to each dose and for two hours after each dose).

Randomization
After you complete radiation therapy, you will return to the clinic to have an MRI and standard blood tests done, including a complete blood count (CBC) and a complete metabolic panel (CMP) to test your liver and kidney function. At this clinic visit, you will be randomly assigned (like drawing numbers from a hat) to be in one of three different groups in the study. All groups in the study will receive up to 10 injections of the study vaccine, called pp65 CMV dendritic cells (DC). The groups differ in the type of pre-conditioning received prior to the fourth DC vaccine (DC vaccine #4). Pre-conditioning refers to something meant to stimulate the immune

system prior to the vaccine. In this study, the pre-conditioning is either unpulsed DCs or Td vaccine (Adult Tetanus & Diphtheria). Unpulsed DCs means that the dendritic cells were not "pulsed" or loaded with genetic material called RNA (ribonucleic acid). One of the groups will also receive infusions of the drug Varlilumab.

- Group 1: Unpulsed DC pre-conditioning prior to DC vaccine #4
- Group 2: Td pre-conditioning prior to DC vaccine #4
- Group 3: Td pre-conditioning prior to DC vaccine #4 and Varlilumab infusion at 7 days prior to each DC vaccine (except DC vaccine #2)

Assignment to the 3 groups will be done in a 3:3:2 ratio, meaning more people will be assigned to Groups 1 and 2 than Group 3. If you are assigned to either Group 1 or 2, you and the research team will be blinded as to whether you receive unpulsed DCs or Td as the pre-conditioning agent. This means that neither you nor the study personnel will know which pre-conditioning you will receive prior to DC vaccine #4. If you are assigned to Group 3, you and the study team will not be blinded, and you will know that you are receiving the Td pre-conditioning and Varlilumab infusions.

Td Booster (Adult Tetanus & Diphtheria)
All groups will receive a Td booster immunization as an intramuscular injection in your arm prior to the first pp65 CMV DC vaccine.

Temozolomide (TMZ) Cycles
After you completed radiation therapy, you will receive cycles(s) of the chemotherapy drug TMZ as part of your standard care. The number of TMZ cycles you will receive depends on whether your MGMT gene is methylated or unmethylated. This is determined by tests performed on the tumor tissue obtained from the surgery you had prior to the study. If you have methylated MGMT, you will receive 6-12 cycles of TMZ.

If you have unmethylated MGMT, you will receive 1 cycle of TMZ. Although patients with your type of unmethylated MGMT tumor appear to be less responsive to treatment with TMZ, there is a chance that treatment with TMZ could help shrink your tumor, and by signing this consent form you are choosing not to receive additional cycles of TMZ. There is a risk that the MGMT tumor testing may incorrectly identify your tumor type as unmethylated and result in you forgoing available therapy with TMZ. The rationale for not giving TMZ if your tumor is unmethylated is to prevent the destruction of your immune cells by a chemotherapy, which is not shown to be as helpful for your tumor. Patient with MGMT methylation will receive TMZ, as it is shown to be useful in killing their tumor.

In this study, each TMZ cycle (or "vaccine" cycles if you do not receive TMZ) is about 5 weeks long (about 35 days). The cycle involves taking TMZ every day for 5 days followed by a 23 day

break with no medication. Blood will be drawn prior to each TMZ cycle or "vaccine" cycles if you do not receive TMZ) to check your white blood cells and your liver and kidney function, which is standard for people receiving TMZ.

Dendritic Cell (DC) Vaccines
You will receive all DC vaccine injections with a thin needle that is about 1½ inches long, which will be placed just under the skin (intradermal) in the area below your groin in both the right and left side at each administration session. Each injection will only take a few seconds. After each vaccine, you will have vital signs taken.

All 10 DC vaccines contain dendritic cells "pulsed" or loaded with genetic material called RNA that instructs the DCs to make a protein called pp65 CMV. DC vaccines will be coordinated with the 35-day TMZ cycles (or "vaccine" cycles if you do not receive TMZ). The first 3 DC vaccines will be given during Cycle 1 of TMZ and you will return to clinic every 2 weeks to receive the first 3 vaccines. Cycle 1 of TMZ will be longer than 35 days. DC vaccine #1 will be given around Day 21 of TMZ Cycle 1. Vaccine #2 will be given around Day 35 of TMZ Cycle 1, and DC vaccine #3 will be given around Day 49 of TMZ Cycle 1. You will repeat leukapheresis about 14 days after DC vaccine #3.

If you have methylated MGMT, you will receive additional TMZ cycles. After the first 3 DC vaccines given during Cycle 1 of TMZ, you will receive the DC vaccine injections on Day 21 of each TMZ cycle. If you have unmethylated MGMT, you will not receive additional TMZ cycles, however, you will receive the remaining DC vaccines on Day 21 of each 35-day cycle. You will receive up to 10 vaccines total.

During the study vaccine appointments, you will have clinic visits scheduled every month. At these visits, you will be checked for any side effects and/or symptoms. You will have an MRI of your brain about every 2 months. You will have your blood drawn to check your white blood cells and your kidney and liver function at every standard clinic visit with the Duke Brain Tumor Center. Approximately 6 tablespoons of blood will also be drawn for immunological testing on the day of vaccines #1-6. Blood for immunological testing will also be drawn just prior to Cycle 2 (2 teaspoons).

Pre-conditioning
One day before the DC vaccine #4, you will receive the pre-conditioning, either the Td or unpulsed DCs, depending on which group you are assigned to. If you are in Group 1 or 2, you will be blinded and not know which pre-conditioning regimen you are receiving. If you are in Group 3, you will receive Td pre-conditioning. The pre-conditioning is injected in the same manner as the DC vaccines, just under the skin (intradermal) in the area below your groin. The pre-conditioning is injected in the right side of your groin, and saline (salt water) is injected in the left side.

Six tablespoons of blood for immunologic testing will be collected at the pre-conditioning visit (the day before DC vaccine #4) and on the day of DC vaccine #4. Two teaspoons of blood will be collected for immunologic testing 1 and 2 days after DC vaccine #4. You will also have 6 tablespoons of blood taken for immunologic testing about 7 days after DC vaccine #4 (before the start of Cycle 3).

Varlilumab Infusions (Group 3 only)
If you are assigned to Group 3, you will receive Varlilumab infusions 7 days prior to all DC vaccines (except DC vaccine #2). Varlilumab will be given at a dose of 3 milligram per kilogram intravenously (injected into your vein). Before the Varlilumab infusions on Day 14 of TMZ/vaccine Cycle 1 and 2, you will have approximately 4 tablespoons of blood drawn for immunological testing. As it is an investigational drug, you will need to have the Varlilumab infusion at Duke University Medical Center.

All Groups You will have approximately 4 tablespoons of blood drawn for immunological testing on Day 14 of TMZ/Vaccine Cycle 1.

Follow Up Visits
After you complete the study vaccines, you will no longer be required to continue visits for this study, but you will be followed up for progression and overall survival. The study team will stay in contact with you through periodic phone calls to ask about your health and about any medications you have taken or are currently taking for the treatment of your tumor.

STORAGE OF BLOOD AND TUMOR FOR FUTURE RESEARCH
As part of this study, you are also being asked to allow the study sponsor and PI to store your **unused** blood and tumor samples for future testing to learn more about how the study drug has worked and to further study the immunology of brain tumors. From these unused samples, it might also be possible to learn more about how to better treat other people with your type of primary brain tumor in the future, and for purposes that are not yet known.

The samples will be stored in the Duke Brain Tumor Immunotherapy Program (DBTIP) Laboratory where all other samples from this study are stored. The samples being stored are ONLY for this study. Our animal studies being done in the DBTIP Lab are identifying markers (like CMV) that may help the effectiveness of the study drug, therefore, as other markers are identified, we would like to investigate whether these same markers are found in your unused samples.

If you do not agree to banking of your unused samples, you can still take part in the main research study.

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Withdrawing consent for the storage and future testing of your unused blood and tumor samples will result in destruction of the unused sample. However, if you withdraw your consent after the unused sample has been tested, the test results and the research study/sample-related information must remain in any database(s) that was created for the research study. The reason for this is to comply with regulations that require the sponsor to make data available for review by the FDA or other appropriate regulatory authorities, or if this research is used to support an application for FDA approval to market the study drug.

If you withdraw consent for participation in the main study or are discontinued form the main study, the unused blood and/or tumor samples you provided will continue to be available for storage and future testing unless you also withdraw your consent for this purpose as stated above. If you want to withdraw your permission for the storage of this blood and/or tumor for future testing, we ask that you contact Dr. Desjardins in writing and let her know you are withdrawing your permission for this unused portion of blood to be used for future research. Her mailing address is: Dr. Annick Desjardins, The Preston Robert Tisch Brain Tumor Center, DUMC Box 3624, Durham, NC 27710.

Please **initial** next to one of the statements below to indicate whether or not you agree to allow storage of your unused samples for possible future research as part of this study in the Duke Brain Tumor Immunotherapy Program (DBTIP) Laboratory.

_____ Yes, I agree to allow my unused blood and/or tumor samples to be stored for future
Initials research in the DBTIP Lab.

_____ No, I do not agree to allow my unused blood and/or tumor samples to be stored for
Initials future research in the DBTIP Lab.

WHAT IF MY TUMOR COMES BACK?
Your tumor may need to be biopsied or removed to confirm that the tumor has, in fact, come back as part of your routine clinical care, outside of this research study. You will be asked to sign a surgical consent form if you have a biopsy or resection (removal of the tumor). If this is clinically indicated and performed here at Duke, it is standard practice to contact you about consenting to provide tissue for research purposes. If you agree to participate in the Duke Brain Tumor Center Biorepository, you will sign a separate research consent and we will use a portion of tissue from your surgery specimen as part of this research study to see how well the immunotherapy worked in that tissue. This sampling includes obtaining histologic slides sampled from the biopsy/resection specimen block to perform immunohistochemistry detection of CMV. Obtained slides will then be stored in the DBTIP lab. We will only receive tumor tissue from this surgery once it has been determined by the pathologist that there is enough tumor tissue to make a pathologic diagnosis. The sampling of biopsy/resection specimens will not exceed 10% of the specimen block so as to preserve adequate tissue should you prefer future diagnostic testing as part of additional clinical trials that you may be enrolled on.

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Please **initial** next to one of the statements below to indicate whether or not you agree to allow the collection of slides from biopsy/resection specimen blocks for detection of CMV studies.

_____ Yes, I agree to allow histologic slides to be obtained from the biopsy/resection
Initials specimen for future research.

_____ No, I do not agree to allow to allow histologic slides to be obtained from the
Initials biopsy/resection specimen for future research.

HOW LONG WILL I BE IN THIS STUDY?
You will receive the DC vaccines monthly (following the first 3 bi-weekly vaccines) for a total of up to 10 DC vaccines. It is approximately 21 months from the time of randomization to DC vaccine #10. If an MRI suggests that the tumor has grown back, you will be offered other treatment options and be removed from the study. We will continue to follow you through periodic phone calls to see how you are doing, indefinitely.

You can choose 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.

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.

Td vaccine (Adult Tetanus & Diphtheria):
With a vaccine, like any medicine, there is a chance of side effects. These are usually mild and go away on their own. Serious side effects are also possible, but are very rare.

Mild Problems following Td
(Did not interfere with activities)
Most Likely

- Pain where the shot was given (about 8 people in 10)
- Redness or swelling where the shot was given (about 1 person in 3)

Likely

- Mild fever (about 1 person in 15)

Less Likely

- Headache or Tiredness (uncommon)

Moderate Problems following Td
(Interfered with activities, but did not require medical attention)

- Fever over 102°F (rare)

Severe Problems following Td
(Unable to perform usual activities; required medical attention)

- Swelling, severe pain, bleeding and/or redness in the arm where the shot was given (rare).

Problems that could happen after **any** vaccine:

- Brief fainting spells can happen after any medical procedure, including vaccination. Sitting or lying down for about 15 minutes can help prevent fainting, and injuries caused by a fall. Tell your doctor if you feel dizzy, or have vision changes or ringing in the ears.
- Severe shoulder pain and reduced range of motion in the arm where a shot was given can happen, very rarely, after a vaccination.
- Severe allergic reactions from a vaccine are very rare, estimated at less than 1 in a million doses. If one were to occur, it would usually be within a few minutes to a few hours after the vaccination.

CMV pp65 DC Vaccine:
The injections may cause an allergic reaction that can include:

Most Likely

- Redness or swelling at the injection site
- Itching

Less Likely

- Hives
- Low-blood pressure
- Difficulty breathing
- In rare occasions death
- It may cause a dramatic increase in the number of immune cells in the brain. This may cause swelling (edema) of the brain. Symptoms of swelling of the brain include:
    - Severe headaches
    - Confusion

- Lack of energy
- Unconsciousness
- Coma
- Loss of movement and/or sensation
- Loss of function in certain areas of the body

- The pp65 DC CMV vaccine may activate the immune system to such a high degree that the immune system may start to attack normal brain tissue or other tissues in the body. Although this is very unlikely, this type of severe reaction can cause serious injury or death.
- There may be a small risk of infection due to potential contamination of the injection during the manufacturing or mixing process. This may result in redness, swelling, and/or irritation at the injection site, and in extremely rare cases, a severe blood infection that could lead to death.
- There may also be risks with the use of this study drug with the standard of care medications and procedures that you will receive such as the chemotherapy that are not known.

It is possible that additional side effects not previously seen or predicted may occur with the combination of the pp65 CMV DC vaccine and Td toxoid, unpulsed DCs, or Varlilumab; these may be mild or very serious. Please immediately tell the study doctor or study staff if you have any side effects or problems during the study.

Effects on the brain including:

- New or recurrent seizures
- Possible injury to normal brain cells surrounding the tumor, possibly resulting in new or worsening neurological deficit (ability to think, move, feel, speak, see)
- Injury to blood vessels with possible clogging resulting in stroke
- Localized brain swelling with possible headache, nausea and vomiting, new or worsening neurological deficit (ability to think, move, feel, speak, see)

Risks from Localized Brain Swelling:

In the event that you experience brain swelling after you receive DC vaccines due to an inflammatory response, your physician may treat you with a reduced dose of bevacizumab (also known by the brand name Avastin) for the swelling. The dose of bevacizumab you would receive is less than the full dose that is given to treat patients for a recurrence of their brain tumor. Bevacizumab will be administered through the vein approximately every three weeks, and the effects of the bevacizumab on the swelling will be evaluated by your physician after each MRI you receive.

If your physician does not feel it is safe for you to receive bevacizumab, your physician may discuss other interventions with you, including steroids or surgery, to treat the inflammatory response to DC vaccination.

If applicable, risks of bevacizumab (a drug often used for the management of malignant glioma that blocks blood vessel growth; blood vessels "feeding" the tumor are required for the tumor to grow) include: (Note: The risks below are for the standard dose of bevacizumab used to treat recurrent malignant glioma. If your study doctor feels you require bevacizumab, you will receive a dose in the study that is half the standard dose.)

Very Common (20% or more of patients)

- High blood pressure (hypertension), which may cause headache or blurred vision
- Abdominal Pain

Common (4-20% of patients)

- Numbness, tingling or pain in the fingers or toes (peripheral sensory neuropathy)
- 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
- Mucocutaneous bleeding, including 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 jawbone 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)

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)

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.

Temozolomide:

Most Likely

- Loss of appetite
- Nausea and vomiting, especially on the first day of each maintenance cycle
- Constipation
- Decrease in blood cell counts

A decrease in the number of white blood cells may increase your risk of infections. A reduction in the number of platelets may increase the risk of bleeding, and a reduced number of red blood cells may increase fatigue or shortness of breath. Some people who have taken TMZ also had the following side effects:

Likely

- Back, abdominal and/or stomach pain, breast pain
- Diarrhea
- Hair loss
- Dry skin, skin redness, itching and/or rash
- Swelling of extremities
- Inflammation of the mouth, throat and/or sinuses
- Headache, confusion, loss of memory, dizziness, fatigue, fever, and/or weakness
- Anxiety, depression
- Joint and muscle pain
- Abnormal coordination, gait and/or feelings in extremities
- Trouble sleeping or sleepiness
- Change in sense of taste
- Visual changes such as double or blurred vision
- Coughing or shortness of breath, respiratory tract infection
- Urinary incontinence/frequency, urinary tract infection
- Weight increase
- Seizures, hemiparesis (weakness on one side of the body)
- Adrenal hypercorticism (elevated hormone levels)
- Allergic reaction, sometimes severe

Less Likely

- Rarely, unusual ("opportunistic") infections have occurred. Rare cases of erythema multiforme (skin condition) have been reported which resolved after discontinuation of TMZ and, in some cases, recurred upon restarting treatment with TMZ. Another, rare yet serious side effect is liver damage which may cause yellowing of eyes and skin, swelling and may result in liver failure.
- Very rare side effects have included secondary cancers including leukemia and myelodysplastic syndrome (MDS). MDS is a disorder of the bone marrow in which blood cells that do not function normally are produced.

Reproductive studies have not been done with TMZ. Immature sperm and testicular atrophy occurred in studies with rats and dogs, using doses of TMZ 1/4 and 5/8 of the recommended human doses. In animal studies TMZ caused death and multiple malformations in fetal rats and rabbits exposed during pregnancy.

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Varlilumab:

Most Likely (occurring in >20% of patients):
- Fatigue
- Rash
- Rash maculo-papular (type of rash characterized by a flat, red area on the skin that is covered with small confluent bumps)

Likely (occurring in 11-20% of patients):
- Itching
- Nausea
- Diarrhea

Less Likely (occurring in 6-10% of patients):
- Infusion reaction with symptoms including chills, nausea, rash, hot flashes
- Decreased appetite
- Vomiting
- Headache
- Fever

A decrease in the lymphocyte count, a type of white blood cell, has commonly been observed following administration of Varlilumab and has not been associated with symptoms.

Additional Rare events requiring hospitalization or otherwise considered serious:
- Bronchospasm (sudden constriction of the muscles in the walls of the bronchioles, which are the passageways by which air passes)
- Inflammation of the kidney

Additional side effects thought possible:
In laboratory tests, Varlilumab has demonstrated the capacity to activate immune cells that are capable of destroying tumor cells. However, Varlilumab may also activate immune cells and that could cause side effects and/or damage to normal tissue. Varlilumab induced activation of normal immune cells may cause symptoms during or shortly after finishing the Varlilumab infusion. Such symptoms are called infusion reactions and as noted above, have occurred in approximately 8% of patients who were administered Varlilumab. The infusion reactions have generally been mild and resolved with or without treatment. Other symptoms that can be associated with infusion reactions may include low blood pressure, fever, shortness of breath, vomiting, abdominal pain, and rash. Symptoms may be mild to moderate or could be severe and lead to life threatening complications such as renal failure, mental status changes and even death. Because Varlilumab is a protein, it is also possible that you could have an allergic reaction to

Varlilumab with similar signs and symptoms as just described. Therefore, you will be monitored in the clinic for 1 hour after receiving the drug (the usual time frame in which these types of extreme reactions may develop), and afterward, we will remain in contact throughout the study period.

Other types of immune activating antibodies have been tested in people and have had side effects ranging from mild to life threatening. Based on studies of other antibodies that activate the immune system in different ways, the following side effects might also be possible:

- Hair loss, loss of pigmentation (color) in the skin
- Severe inflammation of the gastrointestinal tract (including severe diarrhea, passage of blood, abdominal pain, damage to the lining of the intestine, perforation of the intestine). These events may be serious or life threatening, and may require additional treatments such as treatment with corticosteroids, blood transfusions, intravenous artificial nutrition, and hospitalization. In some cases, sigmoidoscopy, colonoscopy (minimally invasive tests where your doctor inserts a scope in your rectum to look inside you colon or part of it) or surgery may be required.
- Changes in number of the various types of cells in the blood, such as neutrophils (which fight infection) and platelets (which make blood clot),
- Changes in functioning in the organs of the endocrine system: pituitary inflammation/failure (causing weight loss, fatigue, weakness, depression, loss of energy, nausea, vomiting, loss of appetite, and confusion; usually treatable but can rarely be fatal), over or under-activation of the thyroid (hypothyroidism or hyperthyroidism), adrenal insufficiency (if not treated, adrenal insufficiency may result in severe abdominal pains, diarrhea, vomiting, muscle weakness and fatigue, depression, extremely low blood pressure, weight loss, kidney failure, changes in mood and personality, and shock) and decreased function of the testes or ovaries (causing loss of sexual function/drive, muscle loss, sleep disturbance, mood/mental disorders, loss of bone mass, loss of hair, infertility and other symptoms)
- Inflammation of the eye (causing visual disturbances or pain)

Based on experience with other immune activating antibodies, it is expected that if events listed above were to occur, they would likely be quickly controlled with appropriate therapy. However, it is possible that side effects could potential rapidly worsen and become life-threatening and even cause death. Any delay in treating these side effects may prolong their duration, and make them more difficult to treat. **You should always report any new symptoms during your**

regular study visits, and immediately contact the study doctor if you develop any worrisome symptoms including the following:

Diarrhea:

- An increase by 2 or more bowel movements a day above your normal pattern, especially if they wake you up at night or the urge to move your bowels comes on suddenly. Even if you are not feeling particularly unwell, DO NOT DELAY IN CONTACTING THE STUDY PHYSICIAN OR NURSE.
- ANY blood in the bowel movements, even if there is no diarrhea.
- ANY marked change in bowel habits, either new constipation or diarrhea.

Abdominal (Stomach) pain or tenderness:

- Even if there is no diarrhea, and particularly if the pain is associated with a fever or requires the use of pain medications. Note: narcotic pain relievers used for abdominal (stomach) pain can suppress diarrhea or symptoms of other adverse events – please check with the study physician or nurse before using for abdominal (stomach) pain.

For patients with tumors that express CD27 (found in some cancers of the blood), it is possible that Varlilumab could rapidly kill the tumor cell and cause something called tumor lysis syndrome. This is unlikely to happen with Varlilumab, but if it were to occur it could cause changes in laboratory tests without any associated symptoms, or in severe cases, damage to the kidney or other organs.

It is theoretically possible that Varlilumab could cause leukemia or lymphoma malignancies that express CD27 to grow and therefore worsen the clinical situation. Another theoretical possibility is that Varlilumab may kill normal CD27 expressing immune cells that could result in an increased risk for developing infections, including potentially life-threatening infections. It is unlikely that these theoretical risks will actually occur, because they have not been observed in testing with Varlilumab, including in animal studies.

If you were to require prolonged treatment with immunosuppressive medications, such as corticosteroids, to manage a serious side effect associated with Varlilumab and/or your study vaccine, your body's ability to fight off certain infections (i.e., opportunistic infections) may be lowered. These infections may require treatment with antibiotic or antifungal medications and may be fatal.

Risks of Varlilumab combined with CMV pp65 DC Vaccine:
Varlilumab combined with CMV pp65 DC Vaccine for the treatment of glioblastoma has not been studied in another clinical trial. The side effects of the combination may be similar to what

has been identified in other trials separately evaluating Varlilumab or CMV pp65 DC Vaccine, or the side effects of the combination may be different. There also may be new side effects of the combination that are not yet known that may occur. You should tell your doctor or nurse right away about any possible side effects that you experience with this combination treatment.

Leukapheresis:
Some side effects associated with the leukapheresis procedure may be similar to those experienced during blood donation and include discomfort or a swollen bruise at the site of needle puncture, a slight risk of developing a local infection at the site, and development of a small scar. In addition, there can be light-headedness, fainting, vomiting, and rapid breathing. Some side effects that may occur are unique to the leukapheresis procedure and include chills caused by cooling of the blood when it is contained in the special machine, and tingling and nausea caused by the blood thinning medicine (citrate), which prevents the blood from clotting while in transit within the machine or its tubing. These side effects can be controlled by slowing the rate at which blood is withdrawn, by warm blankets, by changing the amount of the blood thinning medicine, by giving calcium supplements (tablets taken by mouth or liquid administered by vein), or by discontinuing the procedure.

Rarely, the leukapheresis procedure may be associated with loss of blood, breakdown of the blood, clotting of the blood, allergic reactions, accidental addition of air to the blood going back to you, and fluid overload resulting in shortness of breath or fluid loss resulting in decreased blood pressure. If you require a central venous catheter for the leukapheresis procedure, the risks associated with this deeper venous catheter are air in the chest (~6%) due to a punctured lung, bleeding or fluid in the chest (~2%), bleeding under the skin (~0.3%) and infection (~3%). However, procedures have been developed that use ultrasound (US) devices and fluoroscopy to provide imaging of the central veins during catheter placement. The advantages associated with using US and fluoroscopy include detection of exact vessel location, avoiding veins with clots, and guiding the proper placement of the catheter. Only personnel trained in the use of US and fluoroscopy central line placement at Duke will perform these procedures. These procedures involve a small amount of radiation. The radiation exposure from this procedure is similar to the amount of radiation you would get from living in a high altitude city such as Denver for 4 weeks, or taking 9 airplane flights from New York to Los Angeles.

The side effects listed for leukapheresis can usually be controlled and treated by discontinuing the leukapheresis procedure and by providing appropriate and immediate medical care. In addition, there is always the risk that very uncommon or previously unknown side effects may occur or that life-threatening side effects may occur and death may result.

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For those of Reproductive Potential:

Female
Being a part of this study while pregnant may expose the unborn child to significant risks, some of which may be currently unforeseeable. Therefore, pregnant women will be excluded from the study. If you are a woman of childbearing potential, a blood pregnancy test will be done (using 1 teaspoon of blood drawn from a vein by needle-stick), and it must be negative before you can continue in this study. If sexually active, you must agree to use 2 appropriate contraceptive measures for the duration of the study vaccine administration phase and for 6 months afterwards or if you were administered bevacizumab. Medically acceptable contraceptives include: (1) surgical sterilization (such as a tubal ligation or hysterectomy), (2) approved hormonal contraceptives (such as birth control pills, patches, implants or injections), (3) barrier methods (such as a condom or diaphragm) used with a spermicide, or (4) an intrauterine device (IUD). Contraceptive measures such as Plan B(TM), sold for emergency use after unprotected sex, are not acceptable methods for routine use. If you do become pregnant during this study or if you have unprotected sex, you must inform your study physician immediately.

Male
Your participation in this research may damage your sperm, which could cause harm to a child that you may father while on this study. Such harm may be currently unforeseeable. If you are sexually active, you must agree to use a medically acceptable form of birth control in order to be in this study and for the duration of the study vaccine administration phase and for 6 months afterwards and following bevacizumab administration. Medically acceptable contraceptives include: (1) surgical sterilization (such as a vasectomy), or (2) a condom used with a spermicide. Contraceptive measures such as Plan B(TM), sold for emergency use after unprotected sex, are not acceptable methods for routine use. You should inform your partner of the potential for harm to an unborn child. She should know that if pregnancy occurs, you will need to report it to the study doctor, and she should promptly notify her doctor.

The sponsor will ask to follow the results of any pregnancy that occurs in a subject or partner of a male subject.

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.

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Risks of Magnetic Resonance Imaging (MRI) Scans:
If you take part in this research, you will have an MRI. Magnetic resonance imaging (MRI) uses a magnet and radio waves to make diagnostic medical images of the body. 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, you will be excluded from participation in this research study. We will also keep the examination room locked so that no one carrying metal objects can enter while you are in the scanner.

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 with someone in attendance, if you desire.

During most of the MRI scans, a contrast agent called gadolinium will be injected into your blood vessel through a vein in your arm. 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.

Magnetic Resonance Imaging (MRI) Scans:
You will have a number of MRI 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 due to participating in the research. However, if you have concerns about the overall radiation exposure or MRI safety issues, you should discuss them with your physician.

Other Risks:
Subclinical (no signs or symptoms) autoimmunity may occur, although it is extremely unlikely. Autoimmunity is when the immune system responds to your own healthy tissue and cells. This could be secondary to the disease process itself, the surgical procedure, radiation, CMV pp65 DC vaccine, Td toxoid, chemotherapy, the immune response in the brain, or the destruction of tumor cells. Symptoms vary according to the particular disorder and are many; however, some of the symptoms may include, but are not limited to, depression, fatigue, itching/rash, nausea and/or vomiting, diarrhea, cramping, eye irritation/pain/redness/swelling, or various symptoms from

pituitary gland disturbances. You will be monitored throughout the course of the study for any of these symptoms. Symptoms that fail to respond to medical therapy may lead to permanent impairment or even death.

There may be risks, discomforts, drug interactions or side effects that are not yet known.

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. Possible benefits of your participation include improvement in the symptoms of your disease and/or delayed growth of your tumor and/or lengthening the time of your survival, but this cannot be guaranteed. Your disease may worsen while on this study. However, by participating in this study, you will help doctors better understand the side effects caused by the study drugs and whether or not there are potential benefits of the study drugs. 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?
You do not have to participate in this study to receive treatment for your condition. If you decide not to take part in this research study, you will receive treatment(s) as prescribed or agreed upon by your doctor. This may include getting standard treatment for your condition without being in a study.

Instead of being in this study, you have the following alternatives:

- Getting treatment or care for your cancer without being in a study, which could include radiation therapy and TMZ
- Taking part in another study of an investigational drug
- Getting no treatment
- Getting comfort care, also known as palliative care. This type of care helps reduce pain, tiredness, appetite problems and other problems caused by cancer. It does not treat the cancer directly but instead 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 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.

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As part of the study, results of your study-related laboratory tests, x-rays, and procedures may be reported to the NIH and its affiliates. In addition, your records may be reviewed in order to meet federal or state regulations. Reviewers may include representatives from the Food and Drug Administration (FDA), representatives and affiliates of the NIH, Celldex Therapeutics, who supplies the Varlilumab, the Institutional Review Board (IRB), the Duke Cancer Institute (DCI), Duke's Office of Audit, Risk, and Compliance (OARC), the Brain Tumor Center (BTC) Data Safety Monitoring Board, and others as appropriate. If any of these groups review your research record, they may also need to review your entire medical record.

Your tumor and blood samples will be kept and stored at the Duke Brain Tumor Immunotherapy Program (DBTIP) Lab. Maintaining confidentiality is important to DBTIP. All samples will be kept and stored in a secure place. Your sample will be identified by a unique barcode, which means that your name will not be on the sample. However, this barcode can be linked to your unique study identification number, age, gender, ethnic background. Besides protecting your confidentiality, this barcode system will allow the sponsor to destroy your sample in case you change your mind. Your sample will be kept for the duration of the study. After that time, the sample will be destroyed by methods in accordance with laboratory or institution procedures.
As part of this study, you will be asked to have certain tests and scans. Some of these blood tests and MRI scans would have been done as part of your regular care. The study doctor 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 will be reported in the research record for this study. Results of tests and studies done solely for this research study and not as part of your regular care will also be included in your medical record.

The Department of Health and Human Services (HHS) has issued a Certificate of Confidentiality to further protect your privacy. With this Certificate, the investigators may not disclose research information that may identify you in any Federal, State, or local civil, criminal, administrative, legislative, or other proceedings, unless you have consented for this use. Research information protected by this Certificate cannot be disclosed to anyone else who is not connected with the research unless:

1) there is a law that requires disclosure (such as to report child abuse or communicable diseases but not for legal proceedings);
2) you have consented to the disclosure, including for your medical treatment; or
3) the research information is used for other scientific research, as allowed by federal regulations protecting research subjects.

Disclosure is required, however, for audit or program evaluation requested by the agency that is funding this project or for information that is required by the FDA.

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You should understand that a Confidentiality Certificate does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research. If you want your research information released to an insurer, medical care provider, or any other person not connected with the research, you must provide consent to allow the researchers to release it. This means that you and your family must also actively protect your own privacy.

Finally, you should understand that the investigator is not prevented from taking steps, including reporting to authorities, to prevent serious harm to yourself or others.

This study has an external BTC Data Safety and Monitoring Board Plus (DSMBplus). This is a committee external to Duke that looks at the data for overall safety. By signing this consent form, you agree to allow the study team to provide information to the DSMBplus. You will not be identified by name or medical record number. You will be identified by a study number. The study team may provide dates related to your treatment with the study drug or during this study and dates and descriptions of any adverse effects that you may experience.

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 may 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.

Some information collected in research studies is maintained in your medical record. However, for this study that information will be inaccessible until the end of the study, unless your physician(s) decide that it is necessary for your care.

If this information is disclosed to outside reviewers for audit purposes, it may be further disclosed by them and may not be covered by the 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 name or other personal information will not be revealed.

WHAT ARE THE COSTS?
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 whether or not you were in this research study. 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. Annick Desjardins or her designee**.** At your request, a Financial Counselor in the clinic may provide you with an estimate of costs for routine services.

The study will pay for services and procedures that are done solely for research purposes. Please talk with the PI/study team about the specific services and procedures that will be paid for and the ones for which you or your insurance will be responsible.

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.

Celldex will provide Varlilumab free of charge to you while you are taking part in the study. At the end of the study or if you decide to withdraw from the study before it ends, your study doctor may request that you return for a checkup before you stop receiving Varlilumab if she thinks that stopping it suddenly may harm you and may ask you to complete the tests that would ordinarily occur when a person completes the study. Duke will provide the pp65 CMV DC vaccines free of charge to you while you are taking part in the study. Other research-related costs that will be provided free of charge to you while you are taking part in the study are listed below.

Taking part in this study may cost you and/or your insurance company more than the cost of getting regular medical treatment.

The following are research-related costs that will not be charged to you or your insurance:

1. Leukapheresis
2. Td vaccine (Adult Tetanus & Diphtheria) used in preconditioning
3. DC vaccines
4. Varlilumab
5. Immunologic testing on your blood samples

WHAT ABOUT COMPENSATION?
You will receive no compensation for participating 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., or your Duke physicians

or the study sponsor, Celldex Therapeutics, Inc, 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. Desjardins at 919-684-5301 during regular business hours and at (919) 684-8111 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 otherwise entitled, and will not affect your access to health care at Duke. If you do decide to withdraw, we ask that you contact Dr. Desjardins in writing and let her know that you are withdrawing from the study. Her mailing address is Dr. Annick Desjardins, Duke University Medical Center, DUMC Box 3624, Durham, NC 27710. You may be asked to complete the tests that would ordinarily occur when a person completes the study.

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. The sponsor or regulatory agencies may stop this study at any time without your consent. If this occurs, you will be notified and your study doctor will discuss other options with you.

If you agree to allow your tissue or blood 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. Annick Desjardins in writing and let her know you are withdrawing your permission for your identifiable tissue or blood to be used for future research. Her mailing address is Dr. Annick Desjardins, Duke University Medical Center, DUMC Box 3624, Durham, NC 27710. At that time, we will ask you to indicate in writing if you want the unused identifiable tissue or blood destroyed or if your samples (having all identifying information removed that would link the sample to you) could be used for other research.

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.

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A description of this clinical trial will be available on https://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.

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, questions, complaints or suggestions about the research, contact Dr. Desjardins at 919-684-5301 during regular business hours and at (919) 684-8111 after hours and on weekends and holidays.

For questions about your rights as a research participant, or to discuss problems, concerns or suggestions related to the research, or to obtain information or offer input about the research, contact the Duke University Health System Institutional Review Board (IRB) Office at (919) 668-5111.

If you have questions about your rights as a research subject or if you have questions, concerns, 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.

DUKE UNIVERSITY HEALTH SYSTEM

Consent to Participate in a Research Study
DERIVe: DC Migration Study to Evaluate TReg Depletion In GBM Patients with and without Varlilumab

IRB APPROVED
AS MODIFIED
Jun 22, 2022

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