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INFORMED CONSENT FOR PARTICIPATION IN RESEARCH ACTIVITIES
Adult Consent Form / Parent Permission Form / Adolescent Assent Form (ages 13-17)

MAIN CONSENT

IRB#13384 - PHASE I STUDY OF CELLULAR IMMUNOTHERAPY USING MEMORY ENRICHED T CELLS LENTIVIRALLY TRANSDUCED TO EXPRESS AN IL13Rα2-SPECIFIC, HINGE-OPTIMIZED, 41BB-COSTIMULATORY CHIMERIC RECEPTOR AND A TRUNCATED CD19 FOR PATIENTS WITH RECURRENT/REFRACTORY MALIGNANT GLIOMA

"You" below refers to you or your child.

I. **PURPOSE OF THIS RESEARCH STUDY**: You have been asked to participate in this research study because you have a brain tumor, called malignant glioma, which has either returned after previous therapy or is no longer responding to therapy. The purpose of this study is to evaluate the safety of taking the investigational drug 'autologous IL13(EQ)BBζ/CD19t$^+$ T cells' (glioma-specific immune cells) as well as to determine the highest possible dose for the treatment of the malignant glioma.

Based on your brain tumor, you will be assigned to one of five groups on the study that is most appropriate for your medical care. The four groups are as follows: (1) biopsy group, (2) resected group, (3) intraventricular group, or (4) or (5) dual delivery groups (tumor and ventricular delivery). The study PI will discuss this decision with you before your surgery.

Another purpose of this research study is to better understand the effects of the investigational drug in the body over time. Your treatment on this study is expected to last 3-10 weeks. Active monitoring on this study is expected to last for about 12 months following your last infusion. Thereafter, your medical condition will continue to be followed indefinitely.

It is anticipated that approximately 92 patients will participate in this study.

II. **BACKGROUND**: Many patients with malignant glioma respond to treatment (show no evidence of disease on standard clinical tests) but then relapse (the tumor starts to grow again). Standard of care treatment options for patients with recurrent or progressive malignant glioma could include surgical tumor resection and/or chemotherapy. The major reason why patients have disease relapse is the ability of some tumor cells to survive chemotherapy and/or radiation therapy. Additional ways of killing tumor cells that may be resistant to chemotherapy and radiation therapy may

improve the outcome of treatment. Immune cells can be engineered to kill glioma cells in the laboratory. This is done by inserting a piece of DNA into the immune cells that allows them to recognize glioma cells. A vector called lentivirus is used to carry the piece of DNA into the immune cell. The DNA is then inserted into the immune cell. The cells are then grown to large numbers in the laboratory and stored for patient treatment. It is not known whether these immune cells will kill glioma tumor cells when given to patients. Because the safety of this investigational drug in humans is not known, steroids will be given to lessen any serious side effects that it may cause.

The process of making your immune cells may take up to 60 days, and is described below:

- Your cells will be collected by a procedure called leukapheresis. This procedure involves collecting your blood and separating your white blood cells from other blood components. If your veins are unable to support this procedure, you may have a temporary catheter placed for central venous access.
- Your cells will be isolated, selected and then enriched using a special device and grown in the laboratory.
- Your immune cells will be treated with a lentiviral vector called IL13(EQ)BBZ-T2A-CD19t_epHIV7 (glioma specific). Lentiviral vectors are a type of virus that can enter cells and can change the way the cell acts. This lentiviral vector is based on HIV, however, all HIV-disease causing components have been removed so the vector cannot give you an HIV infection.

The IL13(EQ)BBZ-T2A-CD19t_epHIV7 lentiviral vector was chosen because it is glioma specific (recognizes IL13Rα2 on glioma cells), and can enter and express its genes in immune cells. The cells collected from you are changed by using the lentiviral vector to insert genetic material into the cells. The lentiviral method of gene transfer was used because it is very efficient at modifying the cells in the culture to be able to recognize and kill glioma cells.

- After adding the new genetic material, the cells are grown to larger numbers. Afterwards, the cells are washed and frozen.
- Your modified cells will be tested to make sure it is safe for use.
- It is not known if these glioma-specific immune cells will recognize or kill glioma cells when given to patients.
- This is the first time these glioma-specific cells are being used in humans. If you are assigned to the intraventricular/dual delivery groups of the study, it will also be the first time these cells are put into the ventricle of the brain.

III. **WHAT WILL BE DONE**: You will receive a series of glioma-specific immune cell infusions following your surgical procedure. At the end of your first three weeks of glioma-specific immune cell infusions (up to 3 infusions), you may be eligible for optional weeks of glioma-specific immune cell infusions (as long as you are eligible and there is investigational drug available). This study requires multiple steps. These steps are listed below in the order they will be performed.

Screening Evaluation: If you agree to participate in this portion of the study, you will be asked to sign this Informed Consent and go through the following steps:

- You will be asked questions about your medical history and any medication that you are currently taking.
- You will have a physical exam including measurement of your neurological function, vital signs (blood pressure, heart rate and temperature), weight and height.
- Blood (3 tablespoons) will be drawn for routine blood tests such as Complete Blood Counts, Differential, Platelet counts, Comprehensive Metabolic panel, and, if you are able to become pregnant, a serum pregnancy test will be done. Additionally, 1 teaspoon of blood will also be drawn for correlative studies.
- Your available MRI/FDG-PET scans will be reviewed by the study PI, physician and/or radiologist. You may have additional scans done as clinically required.
- You may be asked to provide brain tumor tissue samples, which have been obtained in past surgery/surgeries, to test for IL13Rα2 expression (target on glioma cells).
- You will be asked to do the following tests:
    - HIV – Human Immunodeficieny Virus, is the same virus that can cause AIDS and we will need to test your blood sample for HIV as well.
    - TB – Tuberculosis screening test. We will need to test your blood for signs of TB. Results from this test will not impact your ability to participate in the study.

The results of these tests will determine whether you are eligible to begin the study. If you are not eligible, you will be removed from the study and your study PI will discuss alternative treatments with you.

Leukapheresis to Collect Immune Cells: First, you will undergo a leukapheresis procedure at the COH Donor Apheresis Center (DAC) to collect your white blood cells necessary to make the glioma-specific immune cells. Before you begin this procedure a physician or nurse at the DAC will evaluate your veins to see if they can support the procedure. It may be determined that a catheter should be placed to facilitate the leukapheresis procedure. If you need a catheter placement the DAC will provide you with a separate consent form and additional information.

The procedure may take up to 4 hours and the entire appointment may take approximately 4 to 6 hours. You will be asked to sign a separate consent form that describes the procedure and the risks involved in greater detail.

The procedure involves removing blood from one line of the catheter, putting that blood through a machine to collect white blood cells while returning the remainder of the blood to you through the other line of the catheter. Your vital signs (e.g., heart rate, pulse, blood pressure, temperature, and respiratory rate) and blood counts will be monitored during the procedure. The procedure will be stopped if continuing would cause you any harm.

If there are technical issues during the procedure or in the immediate processing of the product so that the product cannot be used to make your glioma-specific immune cells or if a second leukapheresis procedure is unsuccessful, you will be taken off the study and alternative treatments will be discussed with you.

Manufacturing of Glioma-specific immune cells: If enough immune cells are collected, these cells will be sent to a laboratory (T Cell Therapeutics Research Laboratory) where the glioma-specific immune cells will be made. These cells will be processed, selected and enriched using the CliniMACS® device, grown in the laboratory and frozen. Samples of the frozen product will be tested to make sure they are safe for use. This process may take up to 60 days. It is possible that problems may occur while making the glioma-specific immune cells that will make them unsuitable for use. You will be informed if this occurs. You will then be taken off the study, and alternative treatments will be discussed with you.

Surgery and Catheter (Rickham Shunt) Placement: If you decide to take part in this study, you will be asked to sign a separate consent form before surgery to have a catheter placed in the tumor site or in the ventricles in your brain at the time of your surgery. This catheter is called a Rickham shunt catheter. The Rickham catheter is required to deliver the glioma-specific immune cells from a syringe to the tumor site/ventricles in the brain. Depending on which group you are assigned to, the catheter will be inserted into your tumor bed/tumor resection cavity/ventricles of the brain.

Prior to the day of surgery, your vital signs will be noted and blood (5 tablespoons) will be drawn for routine blood tests such as Complete Blood Counts, Differential, the Comprehensive Metabolic panel, and Correlative Research purposes. You will also be asked to complete 2 Quality of Life questionnaires (a list of questions asking how satisfied you are with your life in terms of how you feel and what you are able to do day to day). After your surgery, an MRI and PET scan, each, will be done to make sure the catheter is in the right place. After your surgical procedure, if there is extra tumor tissue not needed by pathology, it will be used for research studies if you agree. The catheter will remain in place at least until the last glioma-specific immune cell infusion has been given.

Needle Placement: A needle connected to a syringe filled with the investigational drug will be inserted into the Rickham catheter at the time of each glioma-specific immune cell infusion. The needle will be used to deliver the glioma-specific immune cells from the syringe to the Rickham catheter and then directly into the tumor site/ventricles in the brain. A new needle will be inserted on each of the infusion days. The needle will then be removed after each infusion is completed.

Investigational Drug Plan: Once you have recovered from your surgery, you will be scheduled for your glioma-specific immune cell infusions. Frozen glioma-specific immune cells will be thawed and prepared on the day of each infusion. Infusions will be given at COH as an outpatient. Up to three glioma-specific immune cell infusions will be given over a period of three weeks.
You will receive a lower dose of glioma-specific immune cells during the first infusion week to check for safety. This will be followed by one higher dose of glioma-specific immune cells for the next two weeks to finish up the first set of three infusions unless you are told otherwise.

At the start of each infusion week, the first day will involve the following steps:

- Blood (1-5 tablespoons) will be drawn to test for complete blood count and chemistry panel (comprehensive metabolic panel) and correlative studies.
- You will have a physical exam; you will be asked how you feel and your activity level.

- You will be asked to complete the two Quality of Life questionnaires.
- Medication (example: Tylenol and Benadryl) will be given about 30 minutes before each glioma-specific immune cell infusion.
- If possible, just before you are given the glioma-specific immune cells, a small amount of fluid will be withdrawn from your Rickham catheter. This fluid will be saved and studied in the laboratory to evaluate changes in the tumor environment.

If, at the time of infusion, you do not meet the eligibility criteria, your infusion may be delayed to allow for your medical issues to be appropriately addressed. Once your medical issues are resolved, you may be assessed for eligibility again before proceeding with the infusion.

- A sterile solution will be manually pushed through the needle to ensure that all of the glioma-specific immune cells go into the tumor site/ventricles. The needle will be removed after each infusion.
- Your vital signs (i.e. heart rate, pulse, blood pressure, temperature, and respiratory rate) will be monitored during the procedure. You will be observed for approximately 3 hours after each infusion. You may be observed longer if you experience any side effects from the infusions.

For the week in between any two infusions, you will have blood drawn (2-3 tablespoons) every two days or so to better assess any toxic responses because of the infused glioma-specific immune cells.

You will also be asked to complete the two Quality of Life questionnaires again.

Medications: Up to 28 days after you receive the first dose of the investigational drug, you should not take other drugs such as systemic corticosteroids, chemotherapy, immunosuppressive agents, immunotherapy, or other investigational agents unless you have discussed taking them with your study PI and have been informed that it would be acceptable to do so. The reason you should not take other medications is that they may have effects on the investigational drug (glioma-specific immune cells). Do not take acyclovir for non-life threatening herpes virus infections. If you have an infection after you receive the glioma-specific immune cells, your study PI will provide treatment according to standard of care.

Optional Additional Infusion Cycles (Treatment): After the first three weeks of glioma specific immune cell infusions, you may be eligible for additional infusions. You will be offered additional weeks of infusions as long as it is determined that you tolerated the first 3 weeks of infusions, and additional infusion doses of your glioma-specific immune cell product is available. Your dose will be determined from your prior infusion experiences, and the dose scheduled for each infusion may increase from your prior T cell infusion. The time between the optional infusions may be determined after discussing the plan with the study PI. You are not required to receive additional glioma-specific immune cell infusions if you do not wish to. You should discuss your options and concerns with your study PI/treating physician before starting any additional infusions. Please note that if you previously had a catheter placed in the tumor bed/tumor cavity, you may need to have a second catheter placed in the ventricles in your brain.

Monitoring Tests/Follow up: After you receive your last infusion of glioma-specific immune cells you will have continued monitoring and testing at the times listed below. If you begin to have side effects after receiving your glioma-specific immune cells and your study PI feels it is necessary, you may have additional monitoring and/or testing until your side effects go away.

At 4 weeks following your last glioma-specific immune cell infusion, MRI and FDG-PET scans may be conducted. Each scan will be performed to better assess the glioma-specific immune cells and tumor activity at the site of infusion. You will also be asked to complete the two Quality of Life questionnaires again.

At 4 weeks following your last glioma-specific immune cell infusion, and then again at 3, 6, 8, 10 and 12 months following your last glioma-specific immune cell infusion, the follow up evaluations will include:

- Physical examination
- Vital signs
- Neurological function
- Blood (3 tablespoons) will be drawn again for routine blood tests such as Complete Blood Counts, Differential Platelet counts and the Comprehensive Metabolic panel. An additional 35 ml will be taken at the same time for appropriate research studies in the laboratory.

At your 3, 6 and 12 month visits following your last glioma-specific immune cell infusion, HIV tests will be done.

Long term Follow Up: The long-term health benefits and risks of receiving genetically-modified cells (such as your glioma-specific immune cells) are not well understood. If you receive your glioma-specific immune cells, you will be asked to participate in a long-term follow-up study at City of Hope. The follow-up will be for up to 15 years after your last immune cell infusion. You will be asked to sign a separate consent for the City of Hope long term follow up protocol. By participating in long-term follow up, you will be asked to have a physical exam at least annually. The physical will include testing for the continued presence of your glioma-specific immune cells (until they are no longer detected) and to provide medical information upon request including, but not limited to, information pertaining to any possible new cancer, unexpected or elevated (becomes worse) medical problems, including hospitalizations and medications. You will be asked about your reproductive health. If you are a woman of childbearing age, you will be asked about menstruation, pregnancy or inability to become pregnant. If you are a male you will be asked if you have fathered a child or have been unable to father a child. If you move during this time, you are asked to give the principal investigator or his/her designee a current address and telephone number so that we can contact you. If questions arise, you may call the principal investigator or his/her designee using the contact information provided in the consent form.

Discontinuation of Participation: There may be circumstances in which your participation in this study may be terminated by the investigator without your consent if it is determined to be in your best interest. Reasons for which you may be removed from the study are:

- if you are too ill to continue,
- if you do not want to continue to follow the required study or clinical appointments,
- if you are a female and become pregnant while on the study or
- if you are a male and do not want to use a medically approved form of birth control.

You may decide to stop at any time. You are asked to tell the study PI if you are thinking about or decide to stop. The study PI will tell you how to stop safely, evaluate any side effects you may be experiencing, and discuss what follow-up care and testing could be most helpful for you. It is unknown whether the investigational drug may be removed from your body once it is given.

Whether the study PI discontinues your participation early or you decide to leave the study early, the study PI will evaluate any side effects you may be experiencing. The study physician will ask questions about any problems or discomfort you may have experienced. You will also be asked about any changes in medication since your last visit. The study PI will discuss what follow-up care and testing could be most helpful for you.

Study Closure: There may be situations in which the study may be stopped. The Institution, City of Hope, or the Food and Drug Administration or other health authorities may stop the study at any time if they believe it is in the best interest of the patients.

Research Tests:
Research Blood Draws: If there is any leftover specimen from the research blood draws, you will be asked if City of Hope may retain this specimen for future research that is yet unknown. You may refuse to allow us to retain this specimen and still receive the investigational drug on this study. Because the significance of these laboratory tests will not be known until the results from all research participants have been analyzed, neither you nor your treating physician will be informed of results and the tests will have no impact on your treatment.

I agree to research blood draws and to also allow leftover blood to be used for research purposes:

☐ Yes ☐ No *Initials*: _____

Tumor Biopsy/Resection: If there is any leftover tissue from the biopsy/resection, you will be asked if we may retain this tissue for future research that is yet unknown. You may refuse to allow us to retain this tissue and still receive the investigational drug on this study. The scientific, diagnostic or medical significance of the research to be done is not known. Neither you nor your treating physician will be informed of your individual results.

I agree to leftover tissue from biopsy/resection to be used for research purposes:

☐ Yes ☐ No Initials: _____

Tumor Cyst Aspirate/Cerebrospinal fluid (CSF): If there is any leftover specimen from the aspirate, you will be asked if we may retain this specimen for future research that is yet unknown.

You may refuse to allow us to retain this specimen and still receive the investigational drug on this study. The scientific, diagnostic or medical significance of the research to be done is not known. Neither you nor your treating physician will be informed of your individual results.

I agree to leftover specimen from tumor cyst aspirate/CSF to be used for research purposes:

☐ Yes ☐ No Initials: _____

Tissue Banking: With your permission, specimens left over after diagnostic and clinical tests and research tests listed above have been completed may be stored and used for future research purposes that have not yet been determined. The scientific, diagnostic and/or medical significance of the research to be done is not known. Therefore, neither you nor your treating physician will be informed of your individual results, and they will not affect your treatment in any way. Some of this research may result in new inventions or discoveries that may be of potential commercial value and may be patented and licensed for the development of new products. Donors of blood, tissue and other biological materials do not retain any property rights to the materials. Therefore, you would not share in any money or other benefits that any entity might receive for these inventions or discoveries. Your decision not to allow storage or future use of your tissue or specimens will not affect your ability to participate in this study.

If you agree to allow your specimens to be used for future research, you can change your mind later. If you change your mind, please ask for the "Withdrawal of Informed Consent for Use of Specimens for Future Research" for IRB #13384 – PHASE I STUDY OF CELLULAR IMMUNOTHERAPY USING MEMORY ENRICHED T CELLS LENTIVIRALLY TRANSDUCED TO EXPRESS AN IL13Rα2-SPECIFIC, HINGE-OPTIMIZED, 41BB-COSTIMULATORY CHIMERIC RECEPTOR AND A TRUNCATED CD19 FOR PATIENTS WITH RECURRENT/REFRACTORY MALIGNANT GLIOMA." Please sign this withdrawal form and send it to the principal investigator of this study at City of Hope. Once City of Hope is notified, your withdrawal will be processed. Your specimens will not be used in any new research. At that time, any of your existing specimens will be destroyed.

I agree to have tissue stored for future research:

☐ Yes ☐ No *Initials*: _____

Request for Autopsy: The investigator will ask your family for permission to perform an autopsy upon your death. Autopsy is a very valuable method for learning more about the good and bad effects of the gene transfer (such as your glioma-specific immune cells). If you are willing to allow this, please discuss this with your family and advise them of your wishes. The investigator may be able to tell you and your family what kind of autopsy information will be most helpful for this study and the procedures involved. (Please note that even if you give permission for an autopsy, your family must also agree). Whether death occurs in a hospital or outside of a hospital, the City of Hope will cover the cost of the autopsy.

IV. **POSSIBLE BENEFITS**: You are not expected to benefit directly from participation in this study. Potential benefit to others may result from the knowledge gained from your participation in this research study.

V. **POSSIBLE RISKS AND DISCOMFORTS**: In addition to killing cancer cells, cancer treatment can damage normal tissues and produce unwanted side effects. You will be monitored closely by routine physical examinations and laboratory tests to see if side effects are occurring. By careful adjustments of dosage and schedule, severe side effects can usually be avoided. The study PI may prescribe medication to help keep side effects under control. Study treatment will be discontinued if serious side effects develop that cannot be otherwise controlled. Side effects usually go away when study treatment is stopped, but occasionally problems can persist and cause serious complications. Sometimes a side effect may be fatal.

Blood Drawing: You may experience discomfort, swelling, bruising and or bleeding where the needle enters unless you have a catheter that can be used. Some people feel dizzy when blood is drawn. Rarely, infection may occur.

HIV testing: Being tested for HIV can make you feel nervous or anxious about the test results. A positive test indicates that you are infected with the HIV virus, but no one knows for certain when, if ever, you will get AIDS or a related condition. Receiving positive results may make you very upset. If other people learn about your positive results, there might be a risk that you could be treated unfairly or badly, and even have trouble obtaining insurance or employment. To the extent permitted by law, the researchers will keep your tests results confidential and will not release them to anyone without your written permission. If you test positive, California law requires health care providers and clinical laboratories to report the HIV test results with your personal identifying information to the local health department.

Risk of False Positive HIV Testing: Because the lentivirus vector contains some proteins related to HIV, it is possible that future HIV testing may be more involved for you. It is possible that simple screening tests could detect antibodies to HIV proteins, or that genetic tests may detect this protein related to HIV and provide a false positive HIV test (for example commercial tests to measure the amount of HIV virus in blood may pick up the vector used to genetically modify your cells). Therefore, should you receive a positive HIV test, the results should be evaluated closely by your physician before they are confirmed as a true positive. Possibly, more sophisticated tests will need to be done to determine your true HIV status. There is no risk of getting HIV from this study, just the risk of requiring more involved HIV testing.

Leukapheresis: While you are connected to the blood-filtering machine, your blood pressure may drop. Some subjects experience shortness of breath, fainting or chills. If this happens, the leukapheresis procedure will be stopped and your will be given additional intravenous (IV, into the vein) fluids. A medication that decreases the amount of calcium is used to thin the blood in the machine when it is being filtered. This medication may cause mild symptoms of low calcium in the blood such as cramps, twitching and numbness of the hands. This can easily be corrected by infusing calcium IV into your vein. Occasionally, the filtering process also removes platelets (the cells that help the blood to clot). Your doctors will be checking your

blood counts every day that a collection is done and will only proceed with the collection if the blood counts are adequate to safely do so.

Rickham catheter: The catheter can become infected. It can require removal and antibiotics. Infection that involves the spinal fluid (meningitis) can be serious. It can be life threatening, or even fatal. Rarely, the catheter can become clogged and require replacement. There is a 1% risk of bleeding that might be life-threatening or even fatal. A City of Hope neurosurgeon will explain in detail the risks of the Rickham placement prior to your surgery. This catheter is necessary for introducing your glioma-specific immune cells into the tumor.

MRI (magnetic resonance imaging): Risks include possible anxiety and claustrophobia related to being placed in the large body scanner; temporary discomfort related to having to lie still during the procedure; and possible pain, infection and bleeding related to venipuncture if contrast dye is used. Because MRI works through a powerful magnetic field, it cannot be done if subjects have a pacemaker, intracranial aneurysm clips or other metal implants (for example, types of implants used in eye surgery or orthopedic [bone] surgery), artificial limbs and other medical devices that contain iron. Also, there is a risk that metal objects coming near the magnet may become dangerous as they are pulled toward the magnet. The magnetic field will stop a watch that is within several yards of the magnet. Severe injury or death can occur when subjects with implanted neurological stimulators undergo MRI scans. You should discuss any metal devices in your body with the study staff. In addition, when having an MRI scan, iron pigments in tattooed eyeliner or in eye makeup can potentially cause temporary skin irritation and/or swelling around the eye. For subjects that need an MRI scan and have reduced kidney function there is a chance of developing "nephrogenic systemic fibrosis," a condition characterized by thickening and itchiness of the skin, stiffening of the joints and possible reduction in the ability to move around. This condition is associated with the MRI contrast agent gadolinium and occurs mostly in subjects with severe kidney disease. The risk to subjects with mild kidney problems is anticipated to be small. You will be questioned and examined, if necessary, to confirm that you may undergo MRI scanning without additional risk. An X-ray may be performed to rule out the presence of a suspected foreign body before the MRI.

FDG-PET Scan: The potential risks when you come in for your FDG-PET scan are hemorrhage (hematoma at injection site), infection (catheter related infection) at the injection site, infection from the foley catheter and an allergic reaction to the injected FDG.

Risks Associated with the Infusion of Glioma-specific Immune Cells: You have been informed that this is the first time these immune cells, genetically modified using a vector called lentivirus, are being used in glioma patients Since this is an investigational drug, you may experience side effects that have not been seen in research participants who received the drug in the past.

Most Likely Side Effects: You may experience temporary cough (or shortness of breath), temporary fever, chills, increased heart rate, and new or increased headache at the time of infusion for which you may be treated with Tylenol and/or Demerol as needed. You may also experience nausea or vomiting. After your glioma-specific immune cell infusion, you may also experience temporary

dry skin, skin rash, injection site reaction. You may also experience fatigue, low blood pressure and reduced alertness or confusion.

Likely and Serious Side Effects: Infusion of your glioma-specific immune cells may cause tumor lysis syndrome (sudden destruction of large numbers of tumor cells).

In most patients, the symptoms from tumor lysis syndrome are mild to moderate in severity and are managed easily. Moderate side effects of tumor lysis syndrome include inflammation of the brain (swelling of the brain tissue or space around the brain). This may cause disorientation (not knowing where you are or what time it is), increased lethargy (the feeling of not wanting to move, or do things), stroke, an increase of preexisting neurological conditions (such as increased lack of mobility, or increased speech difficulties) or onset (start) of new neurological conditions.

However, some patients may experience severe, life-threatening reactions that result from inflammation of the brain (such as coma or uncontrolled seizures). Massive inflammation of the brain is an oncologic emergency, and special precautions must be taken to prevent life-threatening complications.

Premedication with anti-histamine (such as Benadryl), acetaminophen (such as Tylenol) can help prevent mild cytokine release. Antihistamines and acetaminophen can be administered prior to your infusion.

In the event you experience a severe tumor lysis syndrome or cytokine release syndrome after your glioma-specific immune cell infusion and the event is life-threatening to you, your study PI might decide to give you steroids for about two weeks (review the section **Corticosteroids** below) to prevent further cytokine activation and release. These steroids might stop the activity of the redirected immune cells and provide an overall temporary suppression of your immune system.

Your study PI might decide to give you a medication called Tocilizumab (review the section **Tocilizumab** below), which are proteins which block specific cytokines known to be associated with cytokine release syndrome that occurs after some infusions with engineered cells. Use of these medications rather than steroids has been shown in early clinical studies to stop cytokine release syndrome without interrupting the anti-tumor activity of your immune cells.

You should discuss with your physician the risks of a cytokine release syndrome, your treatment options in the event you experience a severe reaction, and the possible results when receiving any treatment to stop the activity of your glioma-specific immune cells.

Unlikely but Serious Side Effects:
There is an unknown possibility that your body may have an immune response against your glioma-specific immune cells. If this occurs, your study PI may also decide to give you drugs such as corticosteroids/IL-6 antagonist Tociluzimab, etc, to reduce any undesired side effects.

Additionally, your glioma-specific immune cells could become contaminated with unexpected bacteria, fungus or viral organisms. These contaminants could cause you to develop an infection,

severe illness and/or death. Your glioma-specific immune cells will undergo strict safety testing prior to infusion to you. If there is any evidence of contamination with organisms, your glioma-specific immune cells will not be given to you.

Since this is an investigational drug, unforeseen side effects are possible, including ones that could be severe or fatal. The greatest unforeseen risk is thought to be lentivirus-associated malignancy, where the lentiviral vector might cause the genetic information of cells to change in a manner that result in tumor formation.

If you are assigned to the intraventricular/dual delivery groups of the study or you switch to that group after receiving the first three immune cell infusions, there is also a potential for unknown risks from ICV (intraventricular) injection using the investigational drug because this is a first in human study using this route of administration.

If the side effects from the immune cell infusions are severe, your study PI will give you steroids to ablate the side effects as a result of the immune cells in your body. Currently, it is not known how effective these medications will be in resolving these side-effects and preventing permanent damage to your body.

Corticosteriods: Corticosteroids are man-made drugs (steroids) that closely resemble cortisol, a hormone that your adrenal glands produce naturally. These steroids help reduce your immune response to foreign objects such your glioma-specific immune cells. Common side effects include increased appetite, weight gain, sudden mood swings, muscle weakness, blurred vision, swollen face, acne, worsening of diabetes, high blood pressure, stomach irritation, nervousness, restlessness, having difficulty sleeping, etc.

Tocilizumab (Actemra): Tocilizumab is a drug that is a protein which can block specific cytokines known to be associated with cytokine release syndrome (possible side effect of genetically modified immune cells such as your glioma-specific immune cells). Use of this medication rather than steroids has been shown in early clinical studies to stop cytokine release syndrome without interrupting the anti-tumor activity of the gene-modified immune cells. Your study PI will decide if you should receive this medication and how much should be given to you, but in most cases only a single or short term dose of this medication will be administered. Some of the most common adverse events associated with the long term use of Tocilizumab have been upper respiratory tract infections, nasopharyngitis (head cold), headache, hypertension (high blood pressure), increased ALT (liver enzyme that can indicate to whether you may be having liver damage).

You should discuss with your study PI the risks of a cytokine release syndrome, your treatment options in the event you experience a severe reaction, and the possible results when receiving any treatment to stop the activity of your glioma-specific immune cells.

Risk to an Unborn or Newborn Child: You cannot participate in this study if you are pregnant or nursing a baby. If you are able to have a child, a serum pregnancy test will be done before treatment. If you are sexually active and capable of bearing or fathering a child, you must use a

medically effective form of birth control while you are on this study. If you or your partner becomes pregnant, or you suspect that you or your partner is pregnant while in this study, notify study PI at once.

Risk of Sterility (Inability to bear or father a child): The risk of sterility as a result of your participation on this study is unknown. Sterility is a known possible side effect from receiving chemotherapy as part of your standard care for glioma and has been described to you in a separate consent form. The effects of genetically-modified immune cells (such as your glioma-specific immune cells) on reproductive organs have not been studied and are therefore unknown. If you wish to have children in the future, discuss with your study PI options available outside of City of Hope for storing reproductive cells. You will be asked to sign a separate consent form explaining this.

VI. **ALTERNATIVES TO PARTICIPATION**: Alternatives to participation include surgery, chemotherapy and radiation. Other options are hospice philosophy care, palliative care or both. You may also choose to receive no further treatment for your disease at this time. Your study PI has discussed alternatives to participation with you.

VII. **CONFIDENTIALITY OF INFORMATION**: Any information learned from this study in which you might be identified will be confidential and disclosed only with your permission. By signing this form, however, you allow the researchers to make your information available to the City of Hope Institutional Review Board (IRB) Office, the Cancer Protocol Review and Monitoring Committee (CPRMC), the Office for Human Research Protections (OHRP), the National Cancer Institute (NCI), the Food and Drug Administration (FDA), National Institutes of Health (NIH), Gateway for Cancer Research, Fortress Biotech/Mustang Therapeutics and other regulatory agencies as required by law. If information learned from this study is published, you will not be identified by name.

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

Genetic Information Nondiscrimination Act (GINA): Because this research involves looking at the DNA and genes in your blood and/or tissue samples, you should be aware that a federal law called the Genetic Information Nondiscrimination Act (GINA), generally makes it illegal for health insurance companies, group health plans, and employers of 15 or more persons to discriminate against you based on your genetic information. Health insurance companies and group health plans may not request your genetic information that we get from this research. This means that they must not use your genetic information when making decisions regarding insurability. Be aware that this federal law will not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance.

VIII. **OFFER TO ANSWER QUESTIONS AND RESEARCH INJURY NOTIFICATION**: The principal investigator, Dr. Behnam Badie, M.D., or a colleague, Dr. _____, responsible for your care or treatment, has offered to and has answered any and all questions

regarding your participation in this research study. If you have any further questions or in the event of a research related injury, you can contact Dr. Behnam Badie, M.D. at (626) 256-HOPE (4673) ext. 67100 or Dr. _____ at (626) 256-HOPE (4673) ext. _____.

IX. **INVESTIGATIONAL DRUG (IND)**: This research study involves the use of an investigational drug called autologous IL13(EQ)BBζ/CD19t+ T cells (your glioma-specific immune cells) registered with the Food and Drug Administration (FDA) by City of Hope.

X. **SPONSOR OF THIS RESEARCH**: City of Hope, Food and Drug Administration, Gateway for Cancer Research and Fortress Biotech/Mustang Bio. Inc. are the sponsors of this study.

XI. **COST TO THE RESEARCH PARTICIPANT FOR PARTICIPATION**: The investigational drug, "autologous IL13(EQ)BBζ/CD19t+ T cells", will be provided free of charge by the sponsors. Should this investigational drug become commercially available during the course of your study, you and/or your insurance carrier may be asked to pay for the costs of the drug.

The standard of care procedures provided to you will be the responsibility of you and/or your insurance carrier. You will be responsible for all copayments, deductibles, and other costs of treatment and diagnostic procedures as set forth by your insurance carrier. You and/or your insurance carrier will be billed for the costs of treatment and diagnostic procedures in the same way as if you were not in a research study.

However, neither you nor your insurance carrier will be responsible for the research procedures related to this study.

If you have questions about what costs are covered by the study sponsor, you may contact the City of Hope Office of Clinical Trials Support Services at (626) 256-4673, ext. 64284.

XII. **PAYMENT TO THE RESEARCH PARTICIPANT FOR PARTICIPATION:** You will not be paid for taking part in this study.

XIII. **EXPLANATION OF TREATMENT AND COMPENSATION FOR INJURY**: It is City of Hope policy that in the event of physical injury to a research participant, resulting from research procedures, appropriate medical treatment will be available at City of Hope to the injured research participant, however, financial compensation will not be available.

XIV. **FINANCIAL DISCLOSURE:** City of Hope holds a commercial interest in IL13(EQ)BBζ/CD19t+ T cells , the drug being studied in this research. The City of Hope Conflict of Interest and Commitment Committee and IRB have reviewed City of Hope's institutional interest in IL13(EQ)BBζ/CD19t+ T cells and found that this is very unlikely to affect how you will be treated or how the study results will be determined. If you have questions about this, please ask the Principal Investigator or contact IRB at (626) 256-HOPE (4673) ext. 62700. You may also contact the City of Hope Conflict of Interest Manager, at (626) 256-HOPE (4673), extension 62084.

Dr. Badie, the Principal Investigator, is an inventor on the ICV delivery method patent licensed to Mustang Bio, Inc., the company that provides the autologous IL13(EQ)BBζ/CD19t+ T cells, you will receive and supports this research. The City of Hope Conflict of Interest and Commitment Committee and IRB have reviewed Dr. Badie's interest in Mustang Bio, Inc. and found that this is very unlikely to affect how you will be treated or how the study results will be determined. If you have questions about this, please ask the Principal Investigator or contact IRB at (626) 256-HOPE (4673) ext. 62700. You may also contact the City of Hope Conflict of Interest Manager, at (626) 256-HOPE (4673).

Dr. Brown, a Co-Investigator, is paid as an advisory board member for Mustang Bio, Inc., the company that provides the autologous IL13(EQ)BBζ/CD19t+ T cells you will receive and supports this research. The City of Hope Conflict of Interest and Commitment Committee and IRB have reviewed Dr. Brown's financial interest in Mustang Bio, Inc., and found that this is very unlikely to affect how you will be treated or how the study results will be determined. If you have questions about this, please ask the Principal Investigator or contact the IRB at (626) 256-HOPE (4673) ext. 62700. You may also contact the City of Hope Conflict of Interest Manager, at (626) 256-HOPE (4673).

Dr. Forman, a Co-investigator, has an intellectual property interest in Mustang Bio, Inc., the company that provides the drug, autologous IL13(EQ)BBζ/CD19t+ T cells, you will receive and supports this research. The City of Hope Conflict of Interest and Commitment Committee and IRB have reviewed Dr. Forman's interest in Mustang Bio, Inc. and found that this is very unlikely to affect how you will be treated or how the study results will be determined. If you have questions about this, please ask the Principal Investigator or contact IRB at at (626) 256-HOPE (4673) ext. 62700. You may also contact the City of Hope Conflict of Interest Manager, at (626) 256-HOPE (4673).

XV. **VOLUNTARY PARTICIPATION WITH RIGHT OF REFUSAL**: Your participation in this research study is voluntary. You are free to withdraw your consent for participation in this study without any loss of benefits, penalty, or interference with any future treatment at City of Hope.

XVI. **IRB REVIEW AND IMPARTIAL THIRD PARTY**: This study has been reviewed and approved by the Institutional Review Board (IRB). A representative of that Board, from the Office of Human Research Subjects Protection, is available to discuss the review process or your rights as a research participant. The telephone number of the Office of Human Research Subjects Protection is (626) 256-HOPE (4673) ext. 62700.

XVII. **FINDINGS RELATING TO WILLINGNESS TO CONTINUE PARTICIPATION**: You will be informed of any significant new findings related to this study which might affect your willingness to continue to participate.

EXPERIMENTAL SUBJECT'S BILL OF RIGHTS

The rights below are the rights of every person who is asked to be in a research study. As an experimental subject, you have the following rights:

1. To be told what the research study is trying to find out,

2. To be told what will happen to you and whether any of the procedures, drugs, or devices to be used are different from what would be used in standard practice,

3. To be told about the risks, side effects, or discomforts of the things that will happen to you as part of the research study,

4. To be told if you can expect any benefit from participating in the research study, and, if so, what the benefit might be,

5. To be told of the other choices you have and how they may be better or worse than being in the research study,

6. To be allowed to ask any questions concerning the research study, both before agreeing to be in the study and during the course of the study,

7. To be told what medical treatment is available if any complications arise,

8. To refuse to participate in the research study or to change your mind about participation after the study is started. To be informed that this decision will not affect your right to receive the care you would receive if you were not in the study,

9. To receive a copy of the signed and dated research study consent form,

10. To be free of pressure when considering whether you wish to agree to be in the research study.

SIGNATURE FOR CONSENT: By signing this consent form, you are making a decision to participate in this research study. Your signature on this informed consent form indicates that you:

1. Have read and understood the information in this form.
2. Have had the information in this form explained to you.
3. Have had a chance to ask questions and these questions were answered to your satisfaction.
4. Have been informed that you will receive a copy of this signed consent form, which includes the "Experimental Subject's Bill of Rights."

I hereby agree to be a research participant in this research study:

_____ _____ _____
Research Participant's Signature Date Time
(date and time must be in research participant's handwriting)

_____
Print Research Participant's Name

PARENT/GUARDIAN SIGNATURE

_____ _____ _____
Parent/Guardian's Signature (if applicable) Date Time
(date and time must be in parent/guardian's handwriting)

_____
Print Parent/Guardian's Name and indicate relationship to participant

_____ _____ _____
Parent/Guardian's Signature (if applicable) Date Time
(date and time must be in parent/guardian's handwriting)

_____
Print Parent/Guardian's Name and indicate relationship to participant

INDIVIDUAL OBTAINING CONSENT SIGNATURE

_____ _____ _____
Signature of Individual Obtaining Consent Date Time

_____
Print Name of Individual Obtaining Consent

FOR USE WITH IRB APPROVED TRANSLATED SHORT/LONG CONSENT FORMS FOR NON ENGLISH SPEAKING PARTICIPANTS ONLY

NOTE: To determine who should sign below, review the guidance document, *Consenting Non English Speaking Research Participants (Pediatric or Adult) – Who Signs What?*

Interpreter: By signing here, I attest that I have acted as interpreter and facilitated this consent process.

_____ _____ _____

Interpreter's Signature Date Time

_____

Print Interpreter's Name

Witness: By signing here, I attest that I witnessed the consent process and that the entire consent form was discussed.

_____ _____ _____

Witness' Signature Date Time

_____

Print Witness' Name

IRB#13384 - PHASE I STUDY OF CELLULAR IMMUNOTHERAPY USING MEMORY ENRICHED T CELLS LENTIVIRALLY TRANSDUCED TO EXPRESS AN IL13Rα2-SPECIFIC, HINGE-OPTIMIZED, 41BB-COSTIMULATORY CHIMERIC RECEPTOR AND A TRUNCATED CD19 FOR PATIENTS WITH RECURRENT/REFRACTORY MALIGNANT GLIOMA

AUTHORIZATION TO USE AND DISCLOSE YOUR PROTECTED HEALTH INFORMATION (PHI) FOR PURPOSES OF THIS STUDY

I. **Purpose of this Authorization**: The information about your health is something that is protected by law and cannot, except for certain purposes, be disclosed (shared) without your permission. As part of this research, you are agreeing to allow City of Hope National Medical Center (City of Hope) to use and share with others your personal health information (PHI), as needed for the research. If you agree to participate in the study named above (called the "Study"), you must sign this consent form in addition to the Study Consent Form.

II. **The Information About You that is Covered By this Authorization**: PHI refers to information that we maintain about you that identifies you and includes the information contained in your medical record. Your medical record consists of information related to your health and the treatment we provide to you, such as your medical history, the results of physical exams, blood tests, x-rays and other diagnostic and medical procedures. If you sign this form, you are allowing City of Hope and the individuals indicated below to use and share any PHI we maintain about you that is required for your participation in the Study.

Certain information about you that is highly confidential is needed for the Study. If you sign this form, you are allowing City of Hope and the individuals indicated below to use and disclose the following highly confidential PHI about you: information about HIV/AIDS testing or treatment (including the fact that an HIV test was ordered, performed or reported, regardless of whether the results of such tests were positive or negative).

III. **Purposes for Uses and Sharing of your PHI; Who Will Use, Share and Receive your PHI**: Your PHI will be used and shared with others for the purpose of doing this research as described in the Study Consent Form. Your PHI will also be used to keep the research sponsor informed about this Study, for reporting to those individuals and authorities responsible for overseeing our research activities to

make sure that the activities are properly conducted, and to report to regulatory agencies as required by the Study.

The people authorized to use and share your PHI for purposes of the Study include the Principal Investigator and the research staff supporting the Study; your City of Hope physicians and the health care team; and the Health Information Management Services Department (Medical Records Department). This also includes any agents or contractors used by these individuals or groups for purposes of conducting or managing this Study. At City of Hope, the Institutional Review Board (IRB) and other City of Hope research regulatory committees will have access to your PHI as necessary to monitor research. In addition, at City of Hope, the Cancer Protocol Review and Monitoring Committee (CPRMC) will have access to your PHI as necessary to monitor research.

You are also allowing your PHI to be shared with the Office for Human Research Protections (OHRP) and with any person or agency as required by law. In addition, certain other regulatory agencies, including, the Food and Drug Administration (FDA) and the National Cancer Institute (NCI) will have access to your PHI.

Use and disclosure of your PHI may also continue for as long as the sponsor (City of Hope, Food and Drug Administration (FDA), Gateway for Cancer Research and Fortress Biotech/Mustang Bio, Inc.) needs to maintain the PHI for purposes of obtaining approval of the drug from the FDA or for other FDA reporting.

This study also involves tissue banking (storing your specimens such as blood or tumor tissue). The tissue banked as part of this study will be kept at City of Hope. The banked tissue will be stored indefinitely. Some of the samples collected may also be sent to the Translational Genomics Research Institute (TGen) or to TGen's clinical laboratory, Ashion Analytics (Ashion) for additional laboratory analysis. TGen is a non-profit research institute located in Phoenix, Arizona, that is affiliated with City of Hope. Data generated at TGen or Ashion will be shared with City of Hope investigators associated with this study. Personal identifying information (such as your name) will be removed from all samples prior to sharing them with TGen or Ashion.

By signing this consent form, you also authorize disclosure of your PHI by other health care providers outside City of Hope to be given to the City of Hope investigator and/or the City of Hope research team for follow-up purposes. This

follow-up information may include results of laboratory tests, physical examination, radiological tests, and other information about you.

This authorization will allow us to use and share your PHI for the Study. No other additional uses and disclosures other than for the purposes of the Study are included in this authorization. City of Hope's Notice of Privacy Practices will continue to protect your non-Study information. If necessary, another separate permission will be obtained from you for any non-Study uses or sharing of your PHI.

IV. **Expiration of this Authorization**: This authorization to use and share your PHI will expire twenty-five (25) years from the date that you sign this authorization.

V. **Further Sharing of Your PHI**: Your privacy is important, and this is the reason for having rules which control who can use or see your PHI. City of Hope maintains control over your PHI at present, but once we share this information with a third party (for example, an individual or agency outside of City of Hope), then it is no longer possible to maintain the same level of protection. The persons outside our control may not be governed by federal or state privacy laws, and it is possible that they could share your PHI with others for whom you have not given permission.

The information from this Study may be published in scientific journals or presented at scientific meetings, but your identity will be kept confidential.

VI. **Your Rights Under this Authorization**: You may cancel this permission to use and share your PHI at any time by contacting City of Hope's Privacy Officer at (626) 256-HOPE (4673) ext. 64025. You should ask for the **Revocation (Cancellation) of Authorization for Use of Protected Health Information for Research**. Fill this form out and return it as the form instructs. Your cancellation begins when the Health Information Management Department of City of Hope receives this form. If you cancel this authorization to use and share your PHI, you will no longer be able to participate in the Study. This is because the research under this Study cannot be conducted without your PHI.

Once you cancel your permission to use and share your PHI, the researchers and others involved in conducting the Study will no longer be able to use or share your PHI for this research. PHI already used and shared up to this point as part of this

Study will continue to be used for purposes of this research. This means that any uses of your PHI and any PHI shared about you by City of Hope prior to receiving your cancellation (revocation) form cannot be taken back. While no further PHI about you will be shared for the Study, your PHI already shared will continue to be used in the overall Study.

VII. <u>Signing this Authorization is Your Choice</u>: Your ability to obtain care at City of Hope will not be affected by your decision to sign this authorization form. You will be able to continue to receive health care at City of Hope if you choose not to sign this authorization form or if you sign this form and later cancel your permission to use and share your PHI.

If you agree to the use and sharing of your PHI, please sign below. You will be given a copy of this authorization form.

_____ _____ _____
Research Participant's Signature Date Time
(date and time must be in research participant's handwriting)

_____
Print Research Participant's Name

PARENT/GUARDIAN SIGNATURE

_____ _____ _____
Parent/Guardian's Signature (if applicable) Date Time
(date and time must be in parent/guardian's handwriting)

_____
Print Parent/Guardian's Name and indicate relationship to participant

_____ _____ _____
Parent/Guardian's Signature (if applicable) Date Time
(date and time must be in parent/guardian's handwriting)

_____
Print Parent/Guardian's Name and indicate relationship to participant

INDIVIDUAL OBTAINING CONSENT SIGNATURE

_____ _____ _____
Signature of Individual Obtaining Consent Date Time

_____
Print Name of Individual Obtaining Consent

FOR USE WITH IRB APPROVED TRANSLATED SHORT/LONG CONSENT FORMS FOR NON ENGLISH SPEAKING PARTICIPANTS ONLY

NOTE: To determine who should sign below, review the guidance document, *Consenting Non English Speaking Research Participants (Pediatric or Adult) – Who Signs What?*

Interpreter: By signing here, I attest that I have acted as interpreter and facilitated this consent process.

_____ _____ _____
Interpreter's Signature Date Time

_____
Print Interpreter's Name

Witness: By signing here, I attest that I witnessed the consent process and that the entire consent form was discussed.

_____ _____ _____
Witness' Signature Date Time

_____
Print Witness' Name