Informed Consent Coversheet

Official Study Title:	PHASE I STUDY OF INTRACRANIAL INJECTION OF T CELLS EXPRESSING HER2-SPECIFIC CHIMERIC ANTIGEN RECEPTORS (CAR) IN SUBJECTS WITH HER2-POSITIVE TUMORS OF THE CENTRAL NERVOUS SYSTEM (ICAR)
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H-31973- PHASE I STUDY OF INTRACRANIAL INJECTION OF T CELLS EXPRESSING HER2-SPECIFIC CHIMERIC ANTIGEN RECEPTORS (CAR) IN SUBJECTS WITH HER2-POSITIVE TUMORS OF THE CENTRAL NERVOUS SYSTEM (ICAR)

Background

In this document "you" signifies either you or your child. You are invited to take part in a research study. Please read this information and feel free to ask any questions before you agree to take part in the study.

You have a type of brain cancer. Because many brain tumors come back after standard therapy, you are being asked to volunteer to take part in a gene transfer research study using special immune cells. You may have already thought about being in this study (when we collected blood to make the cells used in this study). You may even have made a decision about whether to be in the study. If this is true for you, it is important that we give you this information and talk about it before we start you in the study.

The body has different ways of fighting infection and disease. No single way seems perfect for fighting cancers. This research study combines two different ways of fighting cancer: antibodies and T cells. Antibodies are types of proteins that protect the body from infectious diseases and possibly cancer. T cells, also called T lymphocytes, are special infection-fighting immune cells present in the blood that can kill other cells, including cells infected with viruses and tumor cells. Both antibodies and T cells have been used to treat patients with cancers. They have shown promise, but have not been strong enough to cure most patients.

The antibody used in this study is called anti-HER2 (Human Epidermal Growth Factor Receptor 2). This antibody sticks to tumor cells because of a substance on the outside of these cells called HER2. Many types of brain tumors are positive for HER2 and your cancer is HER2 positive. HER2 antibodies have been used to treat people with HER2-positive cancers. For this study, the HER2 antibody has been changed so that instead of floating free in the blood it is now attached to T cells. When an antibody is joined to a T cell in this way it is called a chimeric antigen receptor (CAR). These CAR-T cells seem to be able to kill tumors like the one you have, but they don't last very long and so their chances of fighting the cancer are limited. Therefore, developing ways to prolong the life of these T cells should help them fight cancer.

These HER2-CAR T cells are an investigational product not approved by the Food and Drug Administration.

In the past you have signed a consent form that allowed us to generate HER2-CAR from your own blood. We now want to see if these cells can survive in your blood and affect the tumor after being injected into the tumor or the cavity left in the brain after surgical removal.

This research study is sponsored by Baylor College of Medicine, in Houston, Texas.This research study is funded by Triumph Over Kids Cancer Foundation and Cancer Prevention & Research Institute of Texas (CPRIT).

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.

Purpose
The purpose of this study is to find the largest safe dose of HER2-CAR T cells, to learn what the side effects are, and to see whether this experimental intervention might help patients with brain tumors who volunteer to test this new agent.

Procedures
The research will be conducted at the following location(s):
Baylor College of Medicine, TCH: Texas Children's Hospital, and TMH: The Methodist Hospital.

Up to 40 people with brain tumors may be participating on this study.

Earlier, you gave us blood to make HER2-CAR T cells. These cells were grown and frozen for you to be given into the tumor at the time of tumor recurrence or progression or if the tumor was resistant to treatment. To get the HER2 antibody to attach to the surface of the T cells, we inserted the antibody gene into the T cells. This is done with a virus called a retrovirus that has been made for this study and will carry the antibody gene into the T cell. This virus also helps us find the T cells in your blood after we inject them. To see if there are any long-term side effects of gene transfer, regulatory authorities require us to follow people receiving cells with modified genes. This follow-up could be as long as 15 years or death of the research volunteer.

This is a dose escalation study. This means that at the beginning, patients will be started on the lowest dosing schedule (1 of 3 different levels) of T cells. Once that dose schedule proves safe, the next group of patients will be started at a higher schedule. This process will continue until all 3 dose schedules are studied. If the side effects are too severe, the dose will be lowered or the T-cell infusions will be stopped.

When you enroll on this study, you will be assigned a dosing schedule of HER2-CAR T cells. You will be given three injections of cells two weeks apart into a special catheter that leads to your tumor, the cavity left in the brain after surgical removal of your tumor, or into the fluid-filled space in your brain. If you do not have such a catheter already, one will need to be placed to allow for your treatment on this study. Catheter placement is done by a surgeon and further discussion of the procedures and risks involved in catheter placement will be done separately from this document. If you need to have catheter placement, you will also have some blood collected 2-4 weeks before the catheter placement to make sure that it is safe for you to have the procedure.

The first injection of cells you receive will be the lowest dose. The subsequent injections, depending on your assigned dosing schedule, may be higher than the first. Before you receive each injection, you may be given a dose of Tylenol. Each injection will take between 1 and 10 minutes. You will be admitted for overnight observation after each T-cell injection. The injections of your T cells will be given by the Center for Cell and Gene Therapy at Texas Children's Hospital or Houston Methodist Hospital. The injection of cells will be given either through an intracranial catheter (flexible, tube-like tool used to take fluids out or put fluids into the skull) or through a lumbar puncture (spinal tap using a needle to take fluids out or put

fluids into the lower back). After discharge we will follow you in the clinic or through communication with your primary doctor.

If you have stable disease (the tumor did not grow), there is a reduction in the size of your tumor on imaging studies, or if your disease has progressed but your health status is stable after the start of T-cell injections (at least 6 weeks after), you can receive additional doses of the T cells at 2 to 4 weeks intervals if you wish. Additional doses of T cells will be given at the highest cell dose you received during your initial three cell infusions.

Medical tests before T-cell injection:

Before HER2-CAR T-cell injection, you will receive a series of standard medical tests:

Physical exam
Blood tests to measure blood cells, kidney and liver function
Pregnancy test if you could potentially become pregnant or might be pregnant
Measurements of your tumor by routine imaging studies

Medical tests during and after T-cell injection:

You will receive standard medical tests when you are getting the infusions and after:

Physical exams
Blood tests to measure blood cells, kidney and liver function
Measurements of your tumor by routine imaging studies 6 weeks after the infusion

To learn more about the way the HER2-CAR T cells are working and how long they last in the body, an extra amount of blood, based on your weight, up to a maximum of 60 mL (12 teaspoons) of blood will be taken on the day of the T-cell infusion (before and 1 to 4 hours after the T-cell infusion), 3-4 days after the infusion (this one is optional), 1, 2, 4 and 6 weeks after the T-cell infusion and every 3 months for 1 year, every 6 months for 4 years, then yearly for a total of 15 years. This volume is considered safe, but may be decreased if you are anemic. This sample will be kept in a coded manner so that only the study staff may identify you.

During the time points listed above, if the Tcells are found in your blood at a certain amount, an extra 5ml of blood may need to be collected for additional testing.

If you receive additional T-cell infusions after the first one, you will have the same tests and blood draws as described above.

If you have a tumor biopsy or lumbar puncture to obtain CSF performed any time while you are on the study, a sample of this will be requested for research purposes.

If you develop a second abnormal growth, significant blood or nervous system disorder during the trial, a biopsy sample of the tissue will be tested for research purposes (if a sample can be obtained).

Any leftover samples of tissues may be kept for future research on this study. They may be kept for a long time. They will not be shared with individuals not involved in this study

If you decide to withdraw at any time during the study both samples and data collected during your participation will be maintained.

In the event of your death, we will request permission to perform an autopsy (to include biopsy sample as described above) to learn more about the effect of this experimental treatment on your tumor. Proper consent for an autopsy will be obtained from your next of kin in the event of your death. By signing this consent form, you are not forcing your family to agree to this as this is optional for them.

Research related health information

Authorization to Use or Disclose (Release) Health Information that Identifies You for a Research Study

If you sign this document, you give permission to people who give medical care and ensure quality from Baylor College of Medicine, TCH: Texas Children's Hospital, and TMH: The Methodist Hospital to use or disclose (release) your health information that identifies you for the research study described in this document.

The health information that we may use or disclose (release) for this research includes:

- Information from health records such as diagnoses, progress notes, medications, lab or radiology findings, etc.
- Specific information concerning HIV
- Demographic information (name, D.O.B., age, gender, race, etc.)
- Billing or financial records

The health information listed above may be used by and or disclosed (released) to researchers, their staff and their collaborators on this research project, the Institutional Review Board, Baylor College of Medicine, TCH: Texas Children's Hospital, TMH: The Methodist Hospital, CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS (CPRIT) and their representatives, and TRIUMPH OVER KID CANCER FOUNDATION and their representatives.

Agents of the U.S. Food and Drug Administration may inspect the research records including your health information. Agents of regulatory agencies such as the U.S. Department of Health and Human Services will be permitted to inspect the research records including your health information.

A Data and Safety Monitoring Board will have access to the research records including your health information.

Use or Disclosure Required by Law

Your health information will be used or disclosed when required by law.

Your health information may be shared with a public health authority that is authorized by law to collect or receive such information for the purpose of preventing or controlling disease, injury, or disability and conducting public health surveillance, investigations or interventions.

Baylor College of Medicine, TCH: Texas Children's Hospital, and TMH: The Methodist Hospital are required by law to protect your health information. By signing this document, you authorize Baylor College of Medicine, TCH: Texas Children's Hospital, and TMH: The Methodist Hospital to use and/or disclose (release) your health information for this research. Those persons who receive your health information may not be required by Federal privacy laws (such as the Privacy rule) to protect it and may share your information with others without your permission, if permitted by laws governing them.

Please note that the research involves treatment. You do not have to sign this Authorization, but if you do not, you may not receive research-related treatment. To maintain the integrity of this research study, you generally will not have access to your personal health information related to this research until the study is complete. However, your health information that is necessary to your care will be provided to you or your physician. At the conclusion of the research and at your request, you generally will have access to your health information that Baylor College of Medicine, TCH: Texas Children's Hospital, and TMH: The Methodist Hospital maintain in a designated record set, which means a set of data that includes medical information or billing records used in whole or in part by your doctors or other health care providers at Baylor College of Medicine, TCH: Texas Children's Hospital, and TMH: The Methodist Hospital to make decisions about individuals. Access to your health information in a designated record set is described in the Notice of Privacy Practices provided to you by representatives of the specific institution where you are being enrolled into this research study which are: Baylor College of Medicine, TCH: Texas Children's Hospital, and TMH: The Methodist Hospital.

Please note that you may change your mind and revoke (take back) this Authorization at any time. Even if you revoke this Authorization, researchers, their staff and their collaborators on this research project, the Institutional Review Board, CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS (CPRIT) and their representatives, TRIUMPH OVER KID CANCER FOUNDATION and their representatives, regulatory agencies such as the U.S. Department of Health and Human Services, FDA, Baylor College of Medicine, Data and Safety Monitoring Board, TCH: Texas Children's Hospital, and TMH: The Methodist Hospital may still use or disclose health information they already have obtained about you as necessary to maintain the integrity or reliability of the current research. If you revoke this Authorization, you may no longer be allowed to participate in the research described in this Authorization.

To revoke this Authorization, you must write to: Dr. Nabil Ahmed, 1102 Bates Street Feigin Tower, Suite

This authorization does not have an expiration date. If all information that does or can identify you is removed from your health information, the remaining information will no longer be subject to this authorization and may be used or disclosed for other purposes.

No publication or public presentation about the research described above will reveal your identity without another authorization from you.

Potential Risks and Discomforts

While on this research study you are at risk for side effects from the treatments. There may also be other side effects that we cannot predict. Other drugs will be given to make side effects less serious and less uncomfortable. Side effects may be long lasting or permanent. Some side effects may be life threatening.

You should have recovered from the acute toxic effects of all prior chemotherapy at least 2 weeks before entering this study. One exception is Temozolomide (TMZ), a chemotherapeutic agent used for your disease. You may receive TMZ up to two days before you receive the HER2-CAR T-cell infusion, but you will then have to wait six weeks before you resume therapy with TMZ. You will also have to wait six weeks before resuming any other therapy for your cancer. The risks of stopping TMZ and all other therapies for 6 weeks are not known.

We will carefully observe research volunteers on this experimental intervention and the T-cell infusion will be stopped if serious side effects develop. It is important to know that once we inject T cells, we cannot remove them.

Side Effects of HER2-specific Therapies:

There are several CAR T cell products that are similar to our HER2-CAR T cells that have been given to patients with cancer. Some people who have received these antibodies have had temporary muscle and back pain, fever and chills, shaking, chest pain and labored breathing, wheezing, and nausea or vomiting. These side effects are unlikely in this study where the antibody is stuck to the T cells.

There is one report of a research volunteer who received a dose of HER2-CAR T cells that is 100 X-fold greater than the highest dose on this study into the vein and died 5 days after the T-cell infusion. Since this research volunteer also had received high-dose chemotherapy prior to the T-cell infusion and was given a "T-cell growth factor" called interleukin 2 the death of this research volunteer is most likely due to several factors.

Observed side effects of HER2-specific therapies on the heart in patients with other cancers included decreased heart function. This mainly occurred in patients who had received chemotherapies that are toxic to the heart or who had pre-existing heart disease. Normal brain tissues are known not to express

HER2. To treat the side effects of infused T cells we would give you doses of steroids which we hope would kill the T cells but they may still be able to cause serious damage.

Side Effects of the T cells:

Similar types of T cells have been given to research volunteers with cancers and infections. Usually the volunteers have no problems with the infusions. With the increased doses of T cells, there is a possibility that the harmful effects could increase, though in previous studies we have seen very minimal problems. In some previous research volunteers with large tumors, the cells have caused inflammation leading to headache, fever and flu-like symptoms, as well as swelling within the tumor. This swelling could be potentially dangerous and even life threatening depending on the site of the tumor.

A small percentage of research volunteers that receive this type of therapy develop a life threatening complication known as a cytokine storm. This complication causes high body temperature, increased heart rate, and low blood pressure. This complication can be life threatening. There are treatments for this complication.

In addition, a small percentage of patients, who have received a particular type of T cell that attacks leukemia, a type of blood cancer, have developed drowsiness, sleepiness, or have become unresponsiveness. This complication can also be life threatening. As for CRS, there are treatments available for this complication.

Side Effects of the Gene Transfer:

To get the antibody to attach to the surface of the T cell, we must deliver the gene for the antibody into the T cells. This is done with a virus called a retrovirus that has been made f or this study. The retrovirus has been altered so it should not be able to come out of the T cells and infect other cells. When retroviral vectors enter a normal cell in the body, the gene it carries goes into the DNA (genetic material) of the cell. Human DNA contains thousands of genes. When the retrovirus adds the gene it carries into the human DNA this is called integration. Integration can occur anywhere in DNA and most integration does not harm the cell or the study subjects. However, there is a chance that there may be some parts of human DNA where integration may turn on or off other genes. For example, if it turned on a gene that made a substance that caused the cell to grow it might cause uncontrolled increase in the numbers of cells, which could result in cancer. Conversely, if it turned off a gene that made a substance that limits cell growth, it might have the same effect. There was one study in mice where cancer occurred, but most other animal studies have shown this risk to be very low with the type of retrovirus we are using.

Some patients who have received marrow stem cells modified with retroviral vectors to correct immunodeficiency disorders have developed leukemias that are due to the vectors. To date this has only been seen in patients being treated who have received stem cells treated with retroviral vectors for immunodeficiency conditions. No leukemias or other cancers have been seen in hundreds of patients who have received T cells modified with retroviral vectors. However, the risk of developing cancer is a

risk of receiving products that contain a retroviral vector.

Risks related to the intracranial catheter:

Although unlikely, the most common risks associated with the use of the intra-cranial catheter primarily deal with complications due to malposition or malfunction of the device. Either condition may result in blockage or leakage of the catheter, leading to improper cell delivery. This risk will be minimized by using the proper neurosurgical techniques and by imaging to ensure proper positioning of the catheter in the tumor removal cavity. Less commonly (in less than 1 in 200 patients), infection may develop. In such instances antibiotics will be used and the catheter removed if necessary (an outpatient procedure that carries a low risk of causing bleeding or infection of the central nervous system).

Risk of Blood draws:

Pain/discomfort at the site of the needle stick. Bruising and/or bleeding at the site of the needle stick. There is also a very small risk of infection at the site of the needle stick.

Acetaminophen (Tylenol):

Rarely large doses or long term usage can cause liver damage, rash, itching, fever, lowered blood sugar. These side effects are unlikely at the doses being used for this study.

Risk to fetus - Contraception:

Because of potential or unknown effects of the study on a fetus, pregnant women cannot participate in this study. If you are a woman who could potentially be pregnant or become pregnant, you must have a negative pregnancy test prior to entry into this study.

It is possible that the medicines used in this study could injure a fetus if you or your partner becomes pregnant while taking them. Because of the potential risks involved, you or your partner should not become pregnant while you are participating in this study.

If you are sexually active or become sexually active and can get pregnant or can get your partner pregnant, you and your partner must agree to use one of the following forms of birth control every time you have sex and for (6) months afterwards:

* oral contraceptives ("the pill"),
* intrauterine devices (IUDs),
* contraceptive implants under the skin, or contraceptive injections,
* condoms with foam.

Male partners must use condoms.

Should you become pregnant while on this study, you must immediately notify the study personnel.

The investigator will assist you in finding appropriate medical care. The investigator also may ask to be allowed to continue getting information about your pregnancy. You can choose not to provide this information.

Confidentiality:

There is a small risk for the loss of confidentiality. However, the study personnel will make every effort to minimize the risks.

We will watch you very carefully for any side effects. If there are bad side effects, we will stop the treatment.

There may be unknown risks or discomforts involved. Study staff will update you in a timely way on any new information that may affect your decision to stay in the study. There is a small risk for the loss of confidentiality. However, the study personnel will make every effort to minimize these risks.

Potential Benefits
The benefits of participating in this study may be: that your immune system may begin to kill the cancer cells. This could make the cancer grow more slowly, or get smaller, or go away for a while. This benefit is at best only possible, and may not happen to you. Your participation may help the investigators better understand how the immune system can fight this disease. However, you may receive no benefit from participating.

Alternatives
The following alternative procedures or treatments are available if you choose not to participate in this study: other treatments with chemotherapy, radiation, or surgery; or research studies like this one that use other agents. Your doctor will discuss these other options with you. Additionally, the same alternatives are available if, after participation in this research project, you are not responding to the T cells. You may also choose to receive no further intervention for your tumor. If this is your decision, your doctor will help manage your symptoms and will discuss this with you.

Subject Costs and Payments

You will not be charged for the manufacture or preparation of the HER2 CAR T cells, nor will you be charged for the laboratory studies done to monitor how well these T cells are working and to measure how long they stay in your body as they are being done for research. If you have a pregnancy test done for the study, you will not be charged for this test. You may be charged for some research related costs including the infusion of the product. You or your insurance company are responsible for all standard procedures being done as part of your care related to your cancer. These standard procedures include other evaluations including MRIs and laboratory work (not specified above).

You will not be paid for taking part in this study.

This institution does not plan to pay royalties to you if a commercial product is developed from blood or tissue obtained from you during this study.

Research Related Injury

If you are injured as part of your participation in this study, there are no plans to pay you.

Research personnel will try to reduce, control, and treat any complications from this research. If you are injured because of this study, you will receive medical care that you or your insurance will have to pay for just like any other medical care.

Subject's Rights

Your signature on this consent form means that you have received the information about this study and that you agree to volunteer for this research study.

You will be given a copy of this signed form to keep. You are not giving up any of your rights by signing this form. Even after you have signed this form, you may change your mind at any time. Please contact the study staff if you decide to stop taking part in this study.

If you choose not to take part in the research or if you decide to stop taking part later, your benefits and services will stay the same as before this study was discussed with you. You will not lose these benefits, services, or rights.

The investigator, NABIL AHMED, and/or someone he/she appoints in his/her place will try to answer all of your questions. If you have questions or concerns at any time, or if you need to report an injury related to the research, you may speak with a member of the study staff: NABIL M AHMED at 832-824-4611 during the day and 832-826-0860 after hours.

Members of the Institutional Review Board for Baylor College of Medicine and Affiliated Hospitals (IRB) can also answer your questions and concerns about your rights as a research subject. The IRB office number is (713) 798-6970. Call the IRB office if you would like to speak to a person independent of the investigator and research staff for complaints about the research, if you cannot reach the research staff, or if you wish to talk to someone other than the research staff.

The National Institutes of Health and the National Cancer Institute may have access to your records for research purposes.

ADULT ASSENT (as applicable)
If the person you represent is the one invited to take part in this study, you are signing to give your permission. Each adult who lacks the capacity to consent may agree to take part in a study at his or her own level of understanding. When you sign this, you also note that the person you legally represent understands and agrees to take part in this study according to his or her understanding.

Please print the person name you legally represent here _____.

If your child is the one invited to take part in this study you are signing to give your permission. Each child may agree to take part in a study at his or her own level of understanding. When you sign this you also note that your child understands and agrees to take part in this study according to his or her understanding.

Please print your child's name here _____

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Signing this consent form indicates that you have read this consent form (or have had it read to you), that your questions have been answered to your satisfaction, and that you voluntarily agree to participate in this research study. You will receive a copy of this signed consent form.

Subject	Date
Legally Authorized Representative Parent or Guardian	Date
Legally Authorized Representative - Adult	Date
Investigator or Designee Obtaining Consent	Date
Witness (if applicable)	Date
Translator (if applicable)	Date